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# ANNALS OF INTERNAL MEDICINE

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## HYPERTHYROIDISM AND THIOURACIL

By M VIRGINIA PALMER, *Baltimore, Maryland*

### I INTRODUCTION

IN the past few years an extensive literature has evolved concerning goitrogens and the goitrogenous state. Some of the results are confusing and some are still of unknown significance, because our knowledge of thyroid physiology is incomplete and the concept of the pituitary-thyroid axis is not thoroughly understood. What causes the thyroid gland to function abnormally, and what is affected by this abnormal function? How exclusive is the importance of the thyroid in Graves' disease, and what is the importance of the pituitary-thyroid axis in relation to the adrenal glands, the hypothalamus and the autonomic nervous system, and also to such motivating influences as emotional stress, psychic trauma, and focal infection?

The pathologist understands the histology of the normal thyroid gland and recognizes the characteristics of the toxic gland, as well as its return to a normal appearance after treatment with iodine, but the clinician is at a loss to explain the mechanism of the action of iodine or to give a satisfactory explanation in cases in which the gland shows partial involution to normal—i.e., poor response to iodine—or becomes iodine refractory when operation is delayed.

Probably one reason why our knowledge of thyroid physiology is still inadequate is the general tendency to attach an undue amount of importance to the thyroid and to neglect the equally, if not more, important aspects of extrathyroidal motivation and the pathological functioning of associated endocrine glands, such as the adrenals, pancreas, gonads, parathyroids, and pituitary. It would be of great clinical import to be able to explain and to treat satisfactorily such puzzling problems as recurrent postoperative hyperthyroidism, exophthalmos with and without hyperthyroidism, and states of self-limited hyperthyroidism. It is generally admitted that operation is not the final answer, but until recently no better therapy was

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\* Received for publication May 24, 1944

From the Department of Medicine, University Hospital, Baltimore



available. Deep roentgen-ray therapy gives disappointing results and other measures have been even less successful. Some cases have escaped requiring thyroidectomy because a responsible focus of infection has been found and removed, but such cases are few and the risk of operation in an uncontrolled thyroid state is grave. Some few cases have been successfully tided over one or more exacerbativè phases, but though Graves' disease is cyclic and remittent, such successful management is infrequent.

The study of goitrogens is rewarding for the light it may throw on abnormal thyroid function and also because it seems to offer therapeutic avenues of approach which, though not completely paved, are nevertheless usable.

Following the observations of the MacKenzies<sup>7</sup> on rats treated with sulfaguanidine and the work of Richter and Chisby<sup>12</sup> on thiourea compounds, Astwood<sup>3</sup> tested the goitrogenous effect of a large number of sulfonamides and derivatives of thiourea. He found 2-thiouracil to be the most active compound and used it in the treatment of three patients suffering from thyrotoxicosis. Williams and Bissell<sup>14</sup> have reported a series of nine unselected cases of thyrotoxicosis which were treated with this substance.

During the 10 months preceding this report a group of patients at the University Hospital was under treatment with thiouracil.<sup>†</sup> At the time of this report 50 cases were under observation, 22 of whom had received the drug for a minimum of three months. Only six cases had received it for as long a period as nine months, hence this report is necessarily of a preliminary nature.<sup>†</sup> However, it is felt that sufficient information is available to afford a preliminary estimation of the value of the drug, and also to justify the presentation of selected case reports for the light that they may throw on certain aspects of thyrotoxicosis.

## II MANAGEMENT OF CASES

The 50 cases were unselected. No criteria were set up other than that the patient must be definitely thyrotoxic and the basal metabolic rate must consistently exceed  $+30$  per cent. Five of the patients had had one or more partial thyroidectomies. The range in age was from 14 to 72 years. Eighty per cent of the cases were women. The physical states included young thyrotoxic patients in good condition and persons suffering from long-standing severe thyrotoxicosis with extensive parenchymatous visceral damage. Of the 50 cases 22 had received previous treatment with iodine, with rather unsatisfactory results, 28 cases had received no previous treatment, three of the cases were pregnant, 21 were severe thyrocardiacs by clinical and laboratory standards.

\* The thiouracil was supplied by the Lederle Laboratories, Inc., Pearl River, New York.

† Note added November 25, 1944. The cases in the series treated with thiouracil have now reached a total of 100, some of whom have been under observation for as long as 18 months. The routines of treatment and the conclusions for the group as a whole are essentially the same as presented here.

An effort was made to obtain three determinations of the basal metabolic rate preliminary to treatment with thiouracil, one preceding any medication, one following bed rest and phenobarbital sedation, and one following treatment with bed rest, sedation, and liver and vitamin concentrates. In an attempt to evaluate thiouracil, it was given alone in certain cases without any adjunctive therapy, but it is probable that thiamin chloride, or preferably the whole vitamin B complex, is important, even though in our experience it appeared to have no specific effect in lowering the basal metabolic rate\*. For example, on admission one of the patients had a basal metabolic rate of +65 per cent and seven days later one of +47 per cent. After 10 days of phenobarbital sedation and oral and parenteral administration of massive doses of vitamins, the rate was +67 per cent. In another instance the basal metabolic rate was +116 per cent, after one week of non-specific adjunctive treatment it was +92 per cent and two weeks later had risen to +96 per cent.

So far as possible, urinalyses and white blood cell counts were done every other day. The usual blood chemical tests were made weekly. A patient receiving medical management exclusively remained in the hospital until the basal metabolic rate had undergone a sustained fall and was then allowed to go home on condition that he return for weekly check-ups, which included determinations of the basal metabolic rate, complete blood counts, urinalyses, and determinations of cholesterol and non-protein nitrogen. No case was allowed to leave the hospital until he was on a relatively small maintenance dose of thiouracil and had exhibited no trend toward leukopenia or other adverse reaction during the preceding month.

The series of cases can be divided into a group which received medical management exclusively and a group which was referred to surgery for one of two reasons. (1) If the patient had had a previous colloid goiter which had become toxic, thiouracil was found to cause no diminution in size after the thyroid had returned to its pretoxic state, also, it was found that the size of adenomata was not affected. In such cases as these the gland was removed for cosmetic reasons. (2) If the patient was unable to return to the hospital from his home for proper laboratory follow-up studies, a thyroidectomy was elected rather than the risk of uncontrolled medication.

The medical management of the patient coming to operation is only slightly different from the usual routine, in that operation was planned when the basal metabolic rate had reached one-third to one-half of its pre-treatment value. No effort was made to depress it into the  $\pm 10$  per cent range, since it is believed that physiologic equilibrium is established some time before it is reflected in the basal metabolic rate. Because of its greater

\* Williams et al<sup>15</sup> have followed the levels of thiamin and diphosphothiamin, the biologically active form of thiamin, in the blood of 40 unsclerotic thyrotoxic patients and have found them to be below normal and the pyruvic acid to be elevated. Frazier and Ravdin<sup>16</sup> have observed that the administration of vitamin B complex resulted in a greater reduction in pulse rate, more rapid weight gain, and a shorter preoperative period.

vascularity, a thyroid gland which has been treated with thiouracil is more difficult to remove than one prepared with iodine, but no real difference in bleeding, clotting, and prothrombin times between a thiouracil-treated patient and a normal control has been found either pre- or postoperatively. The few changes in prothrombin time noted have been of improvement as the toxicity was brought under control. Platelet counts were completely in correlation with the general blood picture. All the patients were cross-matched to receive blood on the operating table. Recently vitamin K preparations have been given for three days pre- and postoperatively.

Intravenous glucose was given postoperatively, but the patients were encouraged to drink 2000 cc of liquid during the first 24 hours and were then put on a light soft diet. If atelectasis or any appreciable fever developed in the first 48 hours postoperatively, sodium sulfadiazine was given immediately for its bacteriostatic action and because of its apparent similarity to thiouracil in depressing the production of thyroid hormone and thus minimizing the risk of a thyroid storm.

### III METHOD OF TREATMENT WITH THIOURACIL

From the work of other investigators it is known that thiouracil is quickly absorbed and excreted in the urine. A single oral dose was found<sup>14</sup> to give a maximum blood concentration in 15 minutes, but a trace of the substance was present three days later. The same investigators have reported that most of the drug in weight per cent exists in the white blood cells, the concentrations probably being greatest in the bone marrow, the pituitary, and the adrenal glands.

In this series of cases the dosage schedule was arrived at without following the concentration of thiouracil in the blood, the response of the patient, the basal metabolic rate, and general physical signs were depended upon. The schedule employed at the present time is as follows: thiouracil 0.1 gm every three hours for three days, 0.1 gm every four hours for three to six days, then 0.5 or 0.4 gm daily until there is sustained clinical improvement in the patient. It is probable that 0.6 gm of thiouracil is the optimum maximum daily dose, but good results have been obtained with an initial high saturation and there have been no complications. Usually one can arrive at a maintenance dose of 0.1–0.3 gm daily within three months, but during any intercurrent infection the maintenance requirements have been found to be temporarily elevated.

With each dose of thiouracil 10 gr of bicarbonate of soda are given, since the drug is soluble in an alkaline medium—pH 8.5. Before the procedure of giving soda was adopted, two cases of crystalluria and one of microscopic hematuria were encountered, but since then there have been no renal complications.

Cevitamic acid seemed to counteract in some measure the depressant effect of thiouracil upon the bone marrow. All the patients treated during

the past five months have received 100 mg daily of cevitic acid and also doses of liver extract, even though there was no anemia apparent. Capsules of multivitamin concentrates were given two to three times a day. Varying doses of phenobarbital were given at the beginning of treatment, but could generally be discontinued in two to four weeks, depending on the toxic state.

Every patient now receives thyroxin or desiccated thyroid. It is given in dosages of 1/320 to 1/160 gr of thyroxin or 2 gr of desiccated thyroid at the beginning of treatment to all showing exophthalmos or other eye signs and to non-exophthalmic cases later, after the basal metabolic rate has begun a sustained fall. Frequently during the first week of thiouracil therapy a transient enlargement of the thyroid gland was noted. This could usually be prevented by administration of thyroxin\*. Thyroid preparations given by mouth produce a subjective feeling of well-being which seems to outweigh the disadvantage of an increase of a few points in the basal metabolic rate (see page 359). Thyroxin preparations are also important in the management of pitting edema, a condition which was encountered in variable degree in a number of patients before thyroxin was made part of the routine treatment but which has not been observed since.

With a few recent exceptions (to be described later) no patient received any iodine after thiouracil therapy was begun.

#### IV CASE REPORTS

The following case reports were selected for presentation because they are representative of certain subgroups of thyrotoxicosis.

##### *A Thyrotoxicosis exhibiting poor response to iodine*

*Case 1* M McN (series case 3, figure 1), a 52-year-old white female, had presented a history clearly indicative of thyrotoxicosis for the past nine years and had been rather continuously on Lugol's solution for the past five years. During this time she had had episodes of mild cardiac decompensation and moderate but progressive weight loss. Nervousness, fatigue, and restlessness finally compelled her to accept hospitalization. She was admitted on June 2, 1943 with a diffusely enlarged thyroid and a firm asymmetric enlargement of the upper pole of the right lobe about the size of a walnut. The heart was enlarged, rhythm was regular, the pulse was 132, soft apical and aortic systolic blows were heard over the precordium. The blood pressure was 180 mm Hg systolic and 70 mm diastolic. A fine tremor of the hands, tongue, and eyelids was noted, a tendency to stare, but no exophthalmos, was present. The basal metabolic rate was in excess of +100 per cent.

The patient was given Lugol's solution, deep roentgen-ray therapy over the thyroid, and also adjunctive medication of phenobarbital and concentrated vitamins. After two weeks the basal metabolic rate was still in excess of +100 per cent. The patient was allowed to go home but was continued on the same regimen. She was readmitted to the hospital on September 13, 1943, with essentially the same physical

\* One case was that of a woman who was admitted with a diffusely enlarged toxic thyroid. She had first consulted a physician because of pressure symptoms in the throat. On the fourth day of treatment with thiouracil she developed dysphagia and dyspnea. She was given 2 gr of desiccated thyroid U S P twice a day. In three days the gland returned to its pretreatment size and then became progressively smaller under thiouracil medication.

findings as before, except that a gallop rhythm was present. The pulse was 120 per minute, the blood pressure was 150 mm Hg systolic and 80 mm diastolic, the basal metabolic rate was  $+80$  per cent. Treatment with iodine was discontinued, and administration of thiouracil was begun. Two weeks later the basal metabolic rate was  $+77$  per cent, the patient presented no appearance of thyrotoxicosis and reported that she felt better than at any time in the past 10 years. She was mildly diabetic, but the blood sugar levels were fairly normal on 15 units of protamine zinc insulin before breakfast, however, there was no weight gain even though the diet was increased. The basal metabolic rate, which previously had stayed above  $+100$  per cent decreased precipitously on thiouracil medication to  $+60$ ,  $+50$ , and  $+49$ .

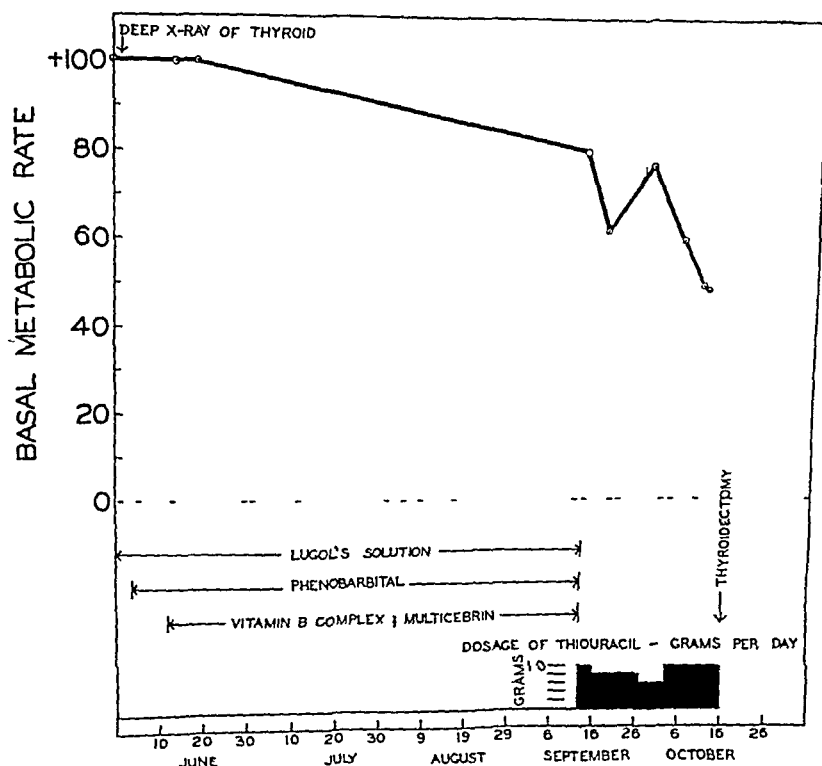


FIG 1 Series case 3. Curve of decline of basal metabolic rate under usual therapy contrasted with decline on thiouracil medication after previous therapy was discontinued. No signs of toxicity were evident notwithstanding the spike in the basal metabolic rate after thiouracil routine had been established. Operation performed when the basal metabolic rate was  $+49$  per cent was without incident.

per cent. An operation was deemed advisable for four reasons: (1) the long-standing thyrotoxicosis had caused progressive myocardial damage, (2) it was feared that the firm adenoma in the right lobe might be undergoing malignant metaplasia, (3) although the diabetes was becoming milder as the thyroid was being brought under control, the patient yet needed a high-carbohydrate diet, which had to be supplemented with insulin, (4) the patient lived in the country and could not be followed at sufficiently frequent intervals if sent home. The operation was approached with some trepidation because the basal metabolic rate was still  $+49$  per cent, physiologically, however, the patient appeared perfectly normal, except for a fine tremor of the extended fingers. The operation was done under avertin-ether anesthesia, and a large substernal extension was found. The vessels over the gland were of pencil

caliber and pulsating actively. The gland was densely adherent to the capsule and the surrounding tissues, probably as a result of deep roentgen-ray therapy. Following operation the maximum pulse rate was 152, the blood pressure was 128 mm Hg systolic and 72 mm diastolic, the rectal temperature did not exceed 100.6° F. Medication consisted of intravenous glucose covered by insulin, phenobarbital, and three doses of 1/6 gr of morphine. On the evening of the second day the patient appeared to have undergone no more physiologic upheaval than that which might be caused by a tonsillectomy, and was able to enjoy a soft diet.

It is inadvisable to draw inferences from one case, but there is an indication here that thiouracil may in some way correct a disordered system not benefited by iodine. There seemed to be good reason to expect some adverse postoperative reaction, but recourse to the time-honored sheet anchor of iodides seemed of questionable safety\*. The response of a patient to thiouracil was found to be retarded by the previous administration of iodine, hence, it was thought that the postoperative administration of iodides might disturb the equilibrium established by thiouracil. No iodides were given, and none seemed to be needed. The patient was walking about on her fifth postoperative day and recovery was uneventful.

*Case 2* L. S. (series case 11, figure 2), a 52-year-old white female, was admitted on October 20, 1943 with complaint of nervousness, loss of weight of 53 pounds during the previous six months, and a growing mass in the neck. In September 1942 she had noticed that she tired easily, was quickly exhausted, and always felt rundown. The menstrual periods became irregular and menorrhagia persisted until early in November. Periods then became normal until May 1943, when amenorrhea occurred. Nausea, vomiting, and burning substernal and epigastric pain appeared in March, and diarrhea persisted intermittently until her admission to the hospital. The patient first noticed a lump in her neck in April and was given some "liquid medicine" by her local physician. Her appetite remained poor and she lost weight steadily because of vomiting and diarrhea. The neck increased rapidly in size, and for the six months prior to her admission to the hospital the patient was conscious of shortness of breath, extreme fatigue, and exertional dyspnea. Six weeks before her admission her family had become so alarmed by her progressive exophthalmos that she was taken to another physician, who put her on Lugol's solution for three weeks, but later discontinued the treatment with iodine and advised hospitalization.

Physical examination at the time of her admission revealed a well-developed middle-aged woman moving restlessly about the bed. There was marked evidence of weight loss, but the skin was soft, moist, and elastic. Her general appearance was remarkable for the stare, the marked exophthalmos, and the diffuse tremor. The eyes presented lid lag and difficulty in convergence, the conjunctiva was injected. The tongue protruded in the midline, was smooth and red, and exhibited a fine tremor. There was marked bilateral enlargement of the thyroid to about 10 times normal size, with a walnut-sized nodule in the right lobe and a slightly smaller one

\* Note added November 25, 1944. There may be a difference in the reaction of the body to the administration of iodine, depending upon whether iodine is given preoperatively along with thiouracil or administered intravenously as sodium iodide at the time of operation when the gland is under a full thiouracil effect and has received no iodine previously. Two recent cases which had been prepared with thiouracil alone were, through an error, given 1 gm of sodium iodide in the operating room. Both cases were returned to the ward in poor condition, with tachycardia, hyperpnea, auricular fibrillation, and beginning hyperpyrexia. On the other hand, this investigator has been informed of a case that seemed to be on the verge of a crisis on the operating table but withstood operation well after receiving intravenous sodium iodide.

The procedure now in use is to give iodine intravenously at operation only if the patient appears to be about to go into a state of crisis. There have been no cases thus far that have presented this appearance.

in the left. A bruit was easily audible. The trachea was deviated to the right and compressed. The heart was enlarged to the left, presenting aortic and mitral systolic blowing murmurs and regular, rapid, forceful, apical beats. The blood pressure was 122 mm Hg systolic and 68 mm diastolic, the pulse rate was 110. Roentgen examination of the chest showed the superior mediastinum to be slightly widened, probably owing to a substernal extension of the thyroid. The basal metabolic rate was found to be +116 per cent, but five days later, after sedation, bed rest, and thiamin chloride therapy, it was down to +92 per cent.

After five days' treatment with 10 gm of thiouracil a day, the patient showed some improvement in that she was less apprehensive and depressed. However, she still displayed the usual manifestations of toxicity, the basal metabolic rate was found

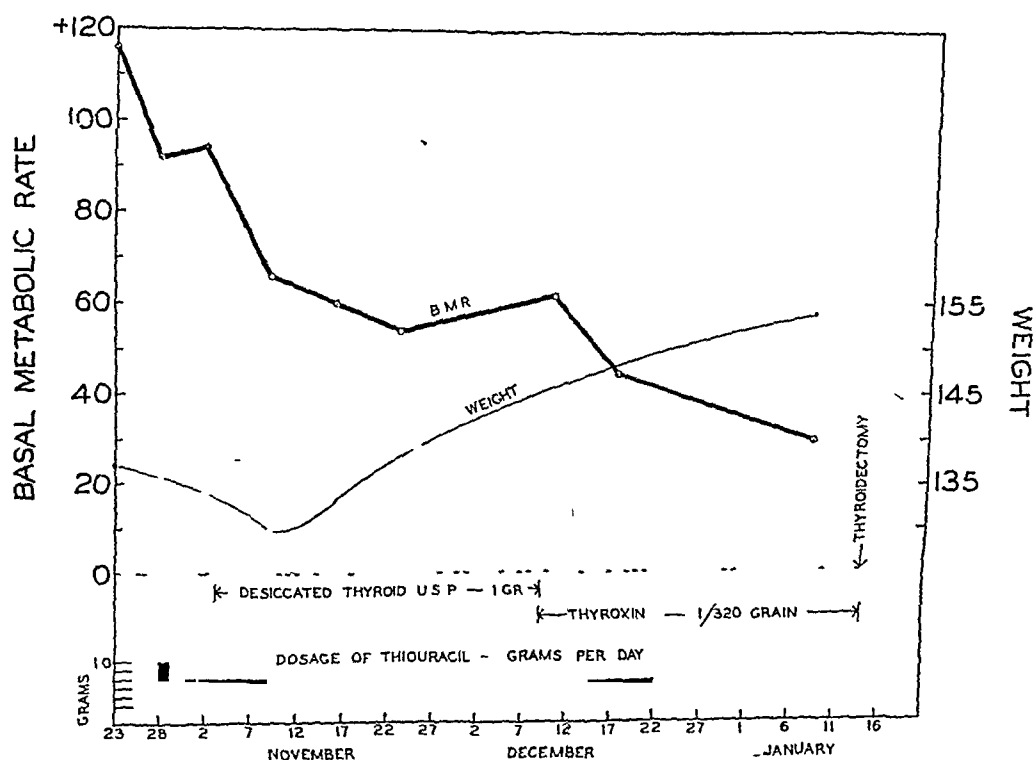


FIG 2 Series case 11. Consistent fall in basal metabolic rate began on the fifth day of thiouracil therapy. Weight gain began in the third week. Thyroxine was substituted for desiccated thyroid because it has a uniform potency. Ophthalmic signs improved when thyroid substance was given. No effect on curve of basal metabolic rate is discernible when thyroid substance was added to thiouracil routine.

to be +94 per cent, and she continued to lose weight. She was given 10 gr of desiccated thyroid daily and the thiouracil dose was reduced to 0.1 gm six times a day. After two weeks of this medication the patient presented many changes: her personality was agreeable and cooperative, she became interested in the people about her and was constantly expressing gratitude over her state of good health and well-being. The exophthalmos was diminishing, although the stare remained. The thyroid gland had decreased in size, but the adenomata were still present. The nodule in the right lobe felt more cystic, that in the left was unchanged to palpation.

Operation was considered advisable because the patient lived a great distance from the hospital and could not be followed satisfactorily at home, also, sufficient thyroid gland remained to produce a marked disfigurement of the neck. The opera-

tion on January 14, 1944 consisted in the removal of two lobes of the thyroid, weighing together 210 gm. The gland was reddish in color, indurated, and irregular in outline. On the cut surface numerous well-defined nodules were seen, no cystic areas were present. The impression of the pathologist was "diffuse and nodular hyperplastic thyroid." The patient withstood the operation extremely well and was able to take a soft diet on the second postoperative day. On the fifth postoperative

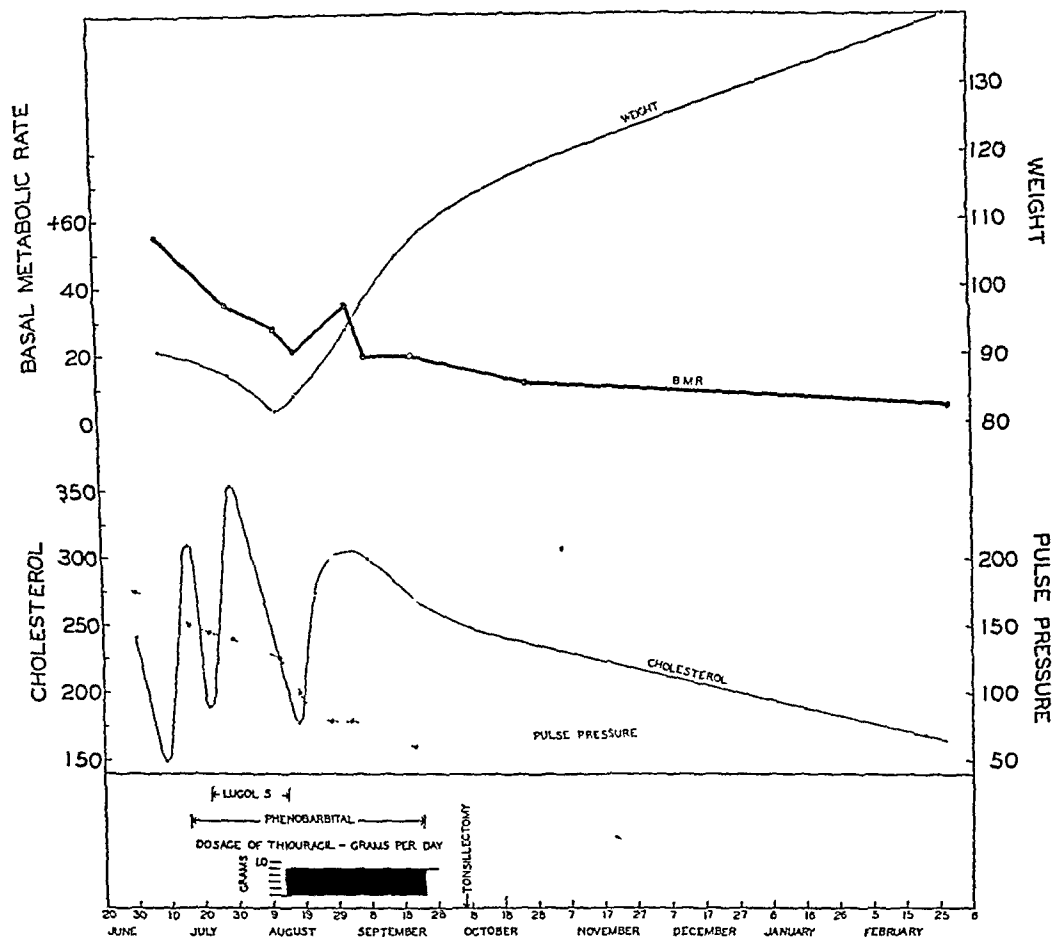


FIG 3 Series case 5 Basal metabolic rate was not determined during first month because of the critical condition of the patient but was brought to +22 per cent by iodine. After thioiracil was started there was a slight transient elevation of the basal metabolic rate to +36 per cent, but after 33 days of thioiracil medication a fall to the previous level obtained on iodine. Weight gain began coincident with thioiracil therapy and pulse pressure showed more rapid improvement. Cholesterol levels did not seem to correlate with improvement of thyroid state.

This patient may be an example of the activating effect of throat infection on latent hyperthyroidism.

day she went into tetany, which was treated successfully with dihydrotachysterol. It is not probable that this complication was related to the previous medication with thioiracil.

### B Hyperthyroidism as a self-limited condition

Case 1 D M (series case 5, figure 3) exemplifies the relationship between acute tonsillitis and sudden fulminating diffuse thyrotoxicosis. This 15-year-old Negro



girl was admitted on June 26, 1943 with an acute illness of three days' duration characterized by headache, abdominal pain, diarrhea, and a jerking of the head synchronous with the pulsations in the neck. Her temperature was 104.4° F, the pulse rate was 143, the blood pressure was 160 mm Hg systolic and 0 mm diastolic. The neck vessels pulsated vigorously enough to shake her entire head, heaving pulsations were also present in the chest and epigastrium. The tonsils were enlarged, hyperemic, and follicular, the posterior cervical glands were enlarged and tender. The thyroid was diffusely enlarged, pulsating, and firm in consistency, a bruit was audible, the overlying skin was erythematous. The heart was full-sized, the rhythm was regular, the sounds were loud and slapping, with a mitral systolic blow and a to-and-fro murmur at the base.

The patient improved with the administration of salicylates, and the impression at that time was that she had rheumatic fever, this diagnosis was supported by electrocardiographic tracings. The blood pressure remained between 130 and 180 mm Hg systolic and 0 mm diastolic. The basal metabolic rate determined one month later was +55 per cent, after the administration of iodine it dropped to +28 per cent and the thyroid decreased in size. The patient was given thiouracil, and the use of iodine was discontinued. On the fourth day of treatment with thiouracil she complained of some burning in the throat and stiffness of the gland, but no objective change in its size or consistency was noted. The basal metabolic rate was found to be transiently elevated between the time the iodine effect had worn off and the thiouracil effect began.

While iodine was being given the patient continued to lose weight, although the pulse pressure was dropping and the heart rate was slowing. She did not show the general physiologic improvement that later was noted on thiouracil, but her subsequent weight gain on thiouracil may have accounted for this impression. On the twenty-second day of thiouracil medication the blood count indicated that the bone marrow was being depressed by the drug. It is now known that the daily dose of 0.8 gm of thiouracil that she had been receiving was too high. The white blood cell count fell to 3900 and the polymorphonuclears showed toxic-degenerative changes. Although the decrease was not sudden and the differential was normal, with polymorphonuclears 64 per cent, lymphocytes 33 per cent, and monocytes 3 per cent, it was not considered advisable to continue the use of the drug. The white blood cell count remained low for three days and then returned to the usual level of 5000. The patient continued to feel well and gained weight. A tonsillectomy was performed and the focus of infection was removed on October 6, 1943. It was then discovered that the patient had been admitted with bilateral retrotonsillar abscesses.

Following tonsillectomy the temperature of the patient rose to 105° F. Thiouracil had been discontinued one week prior to the operation and a course of sulfamerazine had been started. Postoperatively the patient was placed on sulfadiazine, after she developed the high fever. The temperature returned to normal limits on the third day, but the treatment with sulfadiazine was continued for four more days. It was then discontinued because recovery was rapid and uncomplicated. The basal metabolic rate on October 26, 1943 was +12 per cent, on November 16, it was +27 per cent. The weight gain in this period was 10 pounds.

At the time of this report the patient had been at home for five months and was feeling well, but exercise had been restricted because the sedimentation rate remained elevated. The basal metabolic rate on February 28, 1944 was +5 per cent and the weight was 138 pounds. The pulse was 64, the blood pressure was 138 mm Hg systolic and 68 mm diastolic. The electrocardiogram was interpreted as a normal tracing. On May 1, 1944 the basal metabolic rate was still below +10 per cent and the patient weighed 145 pounds—a gain of 65 pounds in weight.\*

\* On November 1, 1944 the basal metabolic rate was +2 per cent and the weight was 145 pounds.

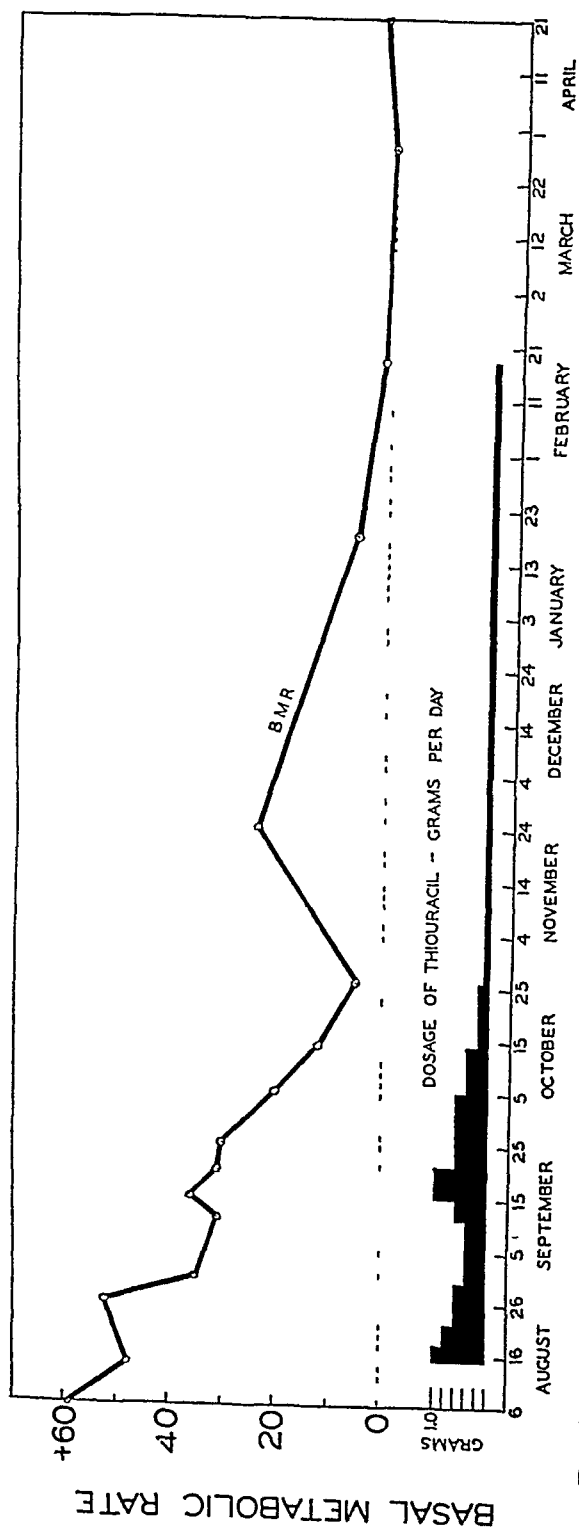


Fig 4 Series case 2 Usual curve of basal metabolic rate on thiouracil treatment Thyroxin 1/160 gr was started November 14 at the time the basal metabolic rate was +24 per cent, because of conjunctival hyperemia, burning, and lacrimation All medication was discontinued on February 18 Two months later the basal metabolic rate was normal

It is entirely probable that the thyrotoxicosis was latent and activated by the tonsillitis, but the tonsillectomy could not have been undertaken safely until the thyroid state had been brought under control. An interesting feature that might be mentioned is the variability of cholesterol levels. There seems to have been no relationship between the serum cholesterol and the hyperthyroid state of the patient.

*Case 2* C A (series case 2, figure 4), a 24-year old white female, was apparently normal until in the last trimester of pregnancy she noticed "jumpiness," some irritability, and a tendency toward insomnia. These symptoms were attributed to her gravid state but became accentuated in the puerperium, and for the next 14 months there was progressive weight loss in spite of an increased appetite. She was admitted to the hospital on August 10, 1943 with complaint of a lump in the neck, difficulty in breathing, and extreme nervousness. The lump in the neck had been noticed for the first time two months previously.

Physical examination revealed a restless young woman with warm moist skin, a fine tremor of the extended fingers, and eyes rather prominent with a tendency to stare. The thyroid was definitely enlarged, with a loud bruit easily audible. The basal metabolic rate was  $+59$  and  $+48$  per cent. The administration of thiouracil and of phenobarbital was begun. The result of the next determination of the basal metabolic rate was  $+52$  per cent, and of the following one (five days later)  $+37$  per cent. The patient reported that she felt much more relaxed on the fourth day of treatment. A weight gain began coincident with treatment and bed rest and was progressive. Contrary to expectation, the basal metabolic rate fluctuated in the  $+30$  per cent range for an unduly long period, in spite of an increase in the dose of thiouracil to 1.0 gm daily. It was found that the diet had been calculated with 150 gm of protein, and the specific dynamic action of this excess protein was considered a contributing factor. The basal metabolic rate dropped 5 per cent shortly after the diet was changed.

The patient began to worry about being away from home, and it was thought that this also might account for the continued elevation of the basal metabolic rate. She gave no appearance of thyrotoxicosis, the only evidence of any abnormality being the high basal metabolic rate. She was discharged from the hospital and sent home with instructions to report at weekly intervals. On the twenty-eighth day of treatment with thiouracil, a painless swelling of the fingers, wrists, feet, and ankles was noticed. At this time the non-protein nitrogen level, albumin-globulin ratio, blood count, and urinalysis were found to be normal. The patient was continued on a dose of 0.6 gm of thiouracil per day. She returned in one week scarcely able to walk because of the extensive edema of the feet and ankles, the basal metabolic rate was  $+20$  per cent\*. In her second week of extensive edema she was found to have a serum chloride level of 310 mg per cent and a carbon dioxide combining power of 50 volumes per cent. The daily dose of thiouracil was reduced to 0.4 gm. Nine days later the patient was still moderately edematous and had a basal metabolic rate of  $+12$  per cent. The dosage of thiouracil was then reduced to 0.2 gm daily, with 5 mg of thiamin chloride three times a day. She returned on October 25, 1943 for a recheck and was found to have a basal metabolic rate of  $+5$  per cent, a serum chloride level of 370 mg per cent, and a carbon dioxide combining power of 65 volumes per cent. There was no edema, the urinalysis was negative, except for four to nine red blood cells, the results of blood counts and blood chemical examinations were normal. The microscopic hematuria was closely followed because a beginning renal complication was suspected, although no such case has so far been reported. Subsequent urinalyses proved negative.

\*Williams and Bissell<sup>14</sup> have reported transient edema in one of their cases which cleared up without discontinuance of the drug. They found an alteration in the serum chloride level and a lowering of the carbon dioxide combining power.

Thiouracil was discontinued on October 29, but three weeks later the basal metabolic rate was found to be +24 per cent, hence the patient was again given 0.1 gm of the drug daily. It was noted that there was some conjunctival injection and an increased tendency to stare, therefore, treatment with 1/160 gr of thyroxin per day was begun at this time. Thereafter the basal metabolic rate was satisfactory and the patient considered herself to be in good health. She was able to carry all of her household responsibilities without undue effort or fatigue. Both thiouracil and thyroxin were discontinued on February 18, 1944. Examination of the patient on May 1, 1944 revealed an apparently fully recovered young woman with no evidence of any thyroid abnormality.\*

The thyroid remained diffusely enlarged throughout the first two and a half months of treatment, it then suddenly began to diminish and was of normal size by the fourth month. No explanation can be given for this reversion of the gland to normal size, other than to remark on the coincidence that the gland began to regress one week after treatment with thyroxin was started. Another interesting point for speculation is the effect that a second pregnancy might have on the endocrine balance of this patient.

### *C Postoperative recurrent hyperthyroidism*

*Case 1* L W (series case 16, figure 5), a 37-year old white male, had had a definite thyrotoxicosis for more than five years. In October and November 1939 he underwent a two-stage thyroidectomy at the University Hospital. One year later exophthalmos developed and with it a return of all of his previous toxic symptoms. He also noticed a marked bronzing of the skin of the legs and feet. In October 1942 he was readmitted for five weeks, and again in January 1943, at which time the basal metabolic rate was +63 per cent. After four months of iodine therapy and supportive treatment, he underwent an operation on May 1, 1943. Because the thyroid was very vascular and the condition of the patient became critical on the operating table, he was returned to the ward after the removal of a small amount of thyroid tissue, the incision was closed a few days later. When readmitted on November 17, 1943 the patient was a thyroid invalid who had been unable to work during the past five years, had had three attacks of cardiac decompensation, and was in imminent danger of developing corneal ulcerations because of the marked exophthalmos. He was started on a course of thiouracil and thyroxin (1/160 gr daily). After one month of hospitalization he was discharged on a maintenance dose of each drug, from that time he worked, gained weight, and also gained self-confidence. There were no cardiovascular symptoms or complaints. On 0.3 gm of thiouracil daily the basal metabolic rate remained below +10 per cent. The dose of thyroxin was increased to 1/160 gr three times a day. The right eye regressed to approximately normal contour, having decreased 5 mm in size, the left eye improved but to a less extent†.

It is probable that this case belongs in the category of the pituitary type of hyperthyroidism. If so, it was unfortunate that thyroidectomy was considered advisable. The patient did not develop severe exophthalmos until after the first operation, thus, at the time of his first admission he seemed to be the usual example of typical Graves' disease presenting, in addition, cardiac arrhythmias and episodes of congestive heart failure. This case and several subsequent ones have corroborated the findings of others<sup>10</sup> that in the pituitary type of hyperthyroidism the basal metabolic rate, if elevated, is easily controlled, thyroidectomy is usually contraindicated, and the chief problem is the control of the exophthalmos.

\* On November 1, 1944 this patient was discharged from further observation.

† Note added November 25, 1944. This patient was last seen on November 15, 1944. He was still on the same routine of treatment, and was at full-time work. The eyes were improving and the bronzing of the skin had disappeared.

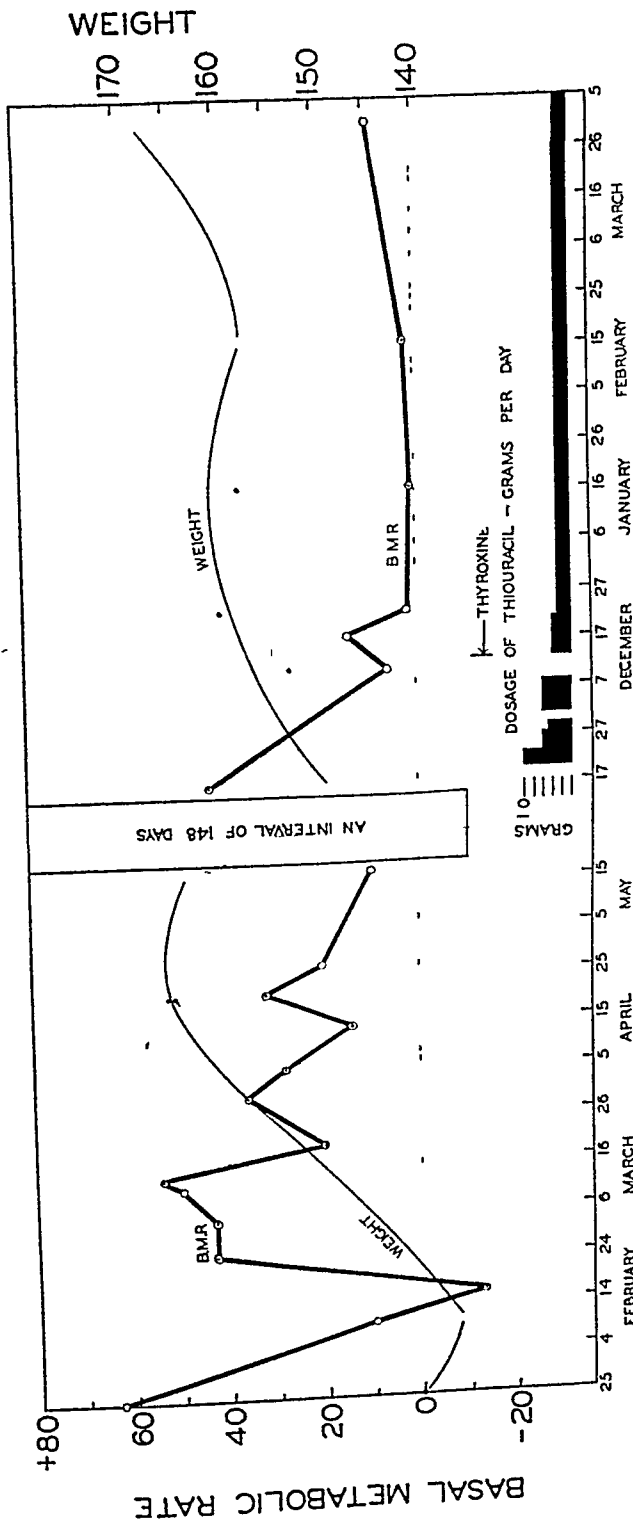


Fig 5 Series case 16 Contrast curves of cyclic variations of basal metabolic rate on iodine therapy with progression of exophthalmos and almost stationary basal metabolic rate on thouracil therapy with increasing dosage of thyroxin but control of exophthalmos

*Case 2 A C* (series case 32), a 30-year old white female presenting the appearance of advanced Graves' disease, was admitted on March 10, 1944 because of premature separation of the placenta in the thirty-second week of pregnancy. Evidence of thyrotoxicosis had been apparent since 1937 and the patient had been on Lugol's solution daily since September 1938. A subtotal thyroidectomy had been performed in December 1938, but relief from symptoms had been only partial and temporary. Early in 1939 she became pregnant and aborted a two months' fetus. Following this her exophthalmos and other signs of thyroid hyperactivity increased and she again underwent a thyroidectomy in May 1939. The patient stated that this gave her no relief of symptoms. She began to have constant headache, some dizziness, and burning and itching of the eyes, and was told that the eyes were becoming larger.

The patient was maintained on 30 minims of Lugol's solution and sedation. Though she continued to be nervous and lost weight, she became pregnant again and was delivered of a full-term living child in September 1941, in spite of a partial premature placental separation. The basal metabolic rate following delivery was +26 per cent. The rate was not determined again until September 1943, when the patient again became pregnant. Throughout the early part of this pregnancy the basal metabolic rate remained at +37 per cent and the patient felt well on 30-45 minims of Lugol's solution daily.

In the thirty-second week of her pregnancy the iodine was discontinued and she was started on thiouracil, the dose being 0.1 gm six times a day, after taking 0.8 gm in 36 hours she developed painless bleeding and was admitted for immediate delivery. The blood pressure on admission was 162 mm Hg systolic and 85 mm diastolic, the pulse was 96. The fetal heart was audible, but when the section was performed the placenta was found free in the uterine cavity and the fetus was dead.

Following operation the patient received 10 gm of sodium iodide intravenously every eight hours for three days and then was maintained on 10 minims of saturated solution of potassium iodide four times a day until March 25, 1944, when treatment with thiouracil was started. The postoperative temperature ranged from 98 to 102° F and the pulse from 80 to 140. The basal metabolic rate on the tenth postoperative day was +59 per cent, on April 1, 1944, after five days of thiouracil medication and no iodine, it was +57 per cent. The patient was given 0.6 gm of thiouracil for the first three days, then 0.5 gm of thiouracil and 1 gr of desiccated thyroid (Armour) for the next five days. She was discharged on a dosage of 0.4 gm of thiouracil and 1/160 gr of thyroxin fraction (Squibb) twice a day. Two weeks later she returned and was found to have a basal metabolic rate of +27 per cent and a weight gain of four pounds. When this paper was written (one month later) she was being maintained on the same dosage of thiouracil and thyroxin fraction with complete relief of symptoms and objective improvement of her exophthalmos, although the basal metabolic rate was still +29 per cent\*.

## V COMMENTS

Figure 6 is a composite graph that is not characteristic of any particular case, but is an average of results obtained in the treatment of 22 cases. Usually the basal metabolic rate dropped steadily from the time treatment was started, but there were many exceptions, some patients even entered the third week of specific treatment with the basal metabolic rate elevated to the

\* Note added November 25, 1944. The basal metabolic rate of this patient is easily maintained within normal limits, but the patient still requires a daily maintenance dose of 0.2 gm of thiouracil and 1/320 gr of thyroxin for control.

initial pretreatment level. This latent period of two to three weeks was noted especially in patients who had been previously treated with iodine.

The rate of metabolism is unaltered as long as the store of thyroid hormone in the gland is adequate, but thiouracil apparently decreases the rate of thyroid hormone synthesis, thus the basal metabolic rate falls as the gland approaches a state of exhaustion. In an untreated toxic gland there is little colloid (figure 7), so the basal metabolic rate falls quickly.

If a patient had been recently treated with iodine, approximately three

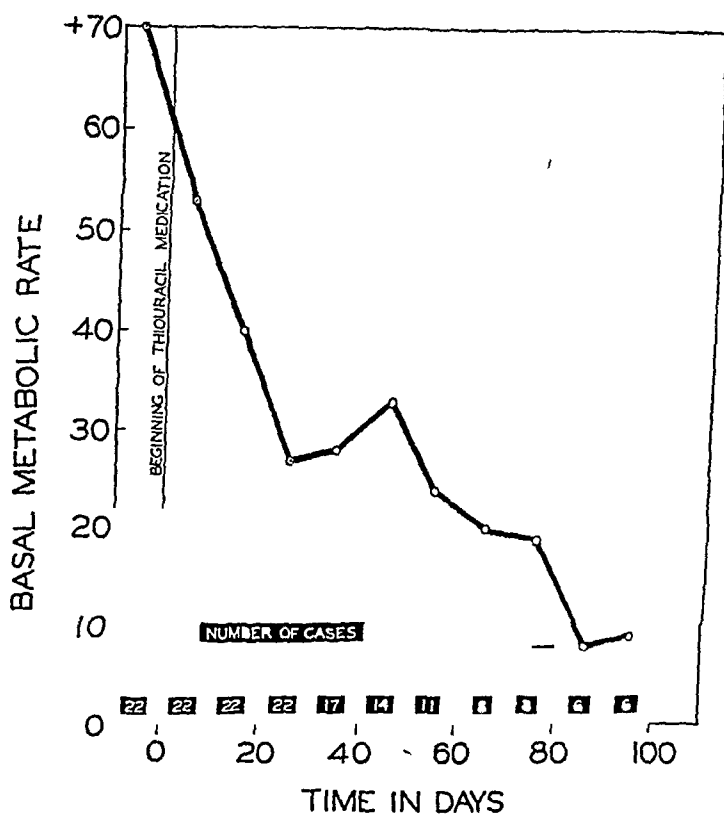


FIG 6 Composite graph representing average basal metabolic rate of first 22 unselected cases in the series. Almost every patient had three determinations of the basal metabolic rate before treatment with thiouracil was started. Adjunctive therapy consisted of high vitamin, high caloric diet, phenobarbital sedation, and in 12 of the cases thyroxin (1/160 gr). Later results were in harmony with this curve.

weeks were required to obtain an equally low basal metabolic rate on thiouracil, but in that interval, even with the basal metabolic rate elevated, the signs of toxicity were less after treatment with thiouracil was started. This feeling of well-being is an interesting feature to be emphasized, because it occurred in practically every case during the first week of thiouracil therapy. Usually the patients remarked spontaneously upon how much better they felt, and always this was in advance of any measurable reduction of the basal metabolic rate.

It is believed that thiouracil does tend to correct a disordered endocrine

equilibrium in a manner different from the action of iodine. This assumption is based partly on the observation that improvement in general physical condition usually preceded a fall in the basal metabolic rate, or was independent of fluctuations of the basal metabolic rate, and partly on the superior response of the 22 cases in the series which were treated with thiouracil after they had received iodine therapy for periods of time ranging from one month to nine years.

The five cases which had had one or more partial thyroidectomy operations and presented persistent or recurrent thyrotoxicosis responded as satisfactorily to thiouracil as did the rest of the group, who had had no

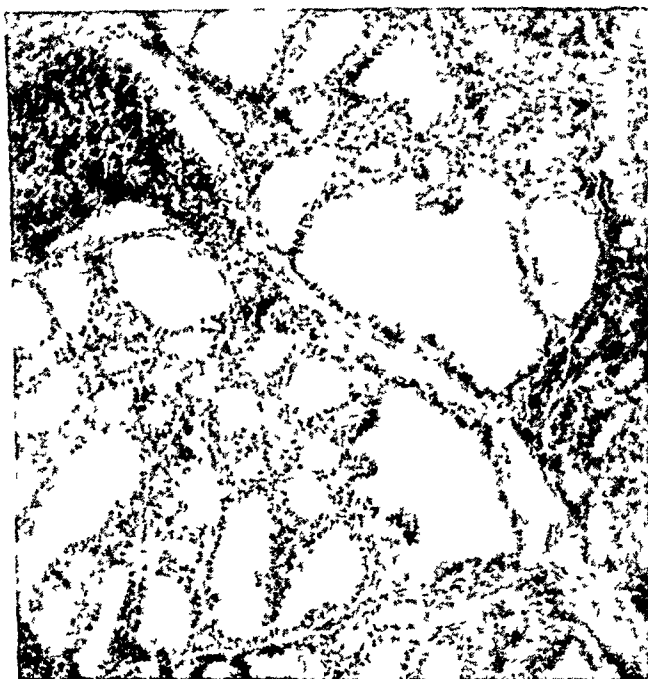


FIG 7 Typical hyperplastic goiter untreated

previous thyroid operation. Nineteen patients, including the above group of five, had a definite stare or actual exophthalmos but the eye signs diminished on thyroxin therapy while concurrently the basal metabolic rate was brought to normal on thiouracil medication. Two cases with exophthalmos were started on treatment with thiouracil alone, but within 24 hours each presented lacrimation, conjunctival hyperemia, and ocular irritation. These symptoms abated within 24 hours after 1/160 gr of thyroxin twice daily was administered. In cases of stare or cases without eye signs no ocular irritation was noted when thyroxin was not made a part of the routine.

In the series of 50 cases, 19 either have completed or are receiving treatment with thiouracil and adjunctive vitamin-sedation-liver therapy. The other 31 are receiving a combination of thiouracil, adjunctive therapy, and



thyroxin The vitamin-sedation component has been found to be of value in building up the depleted energy stores of the patient but has no specific effect on lowering the rate of metabolism

The administration of thyroxin (or desiccated thyroid) was found to have no appreciable inhibitory effect on the action of thiouracil in lowering the basal metabolic rate In cases of exophthalmos in which the two drugs were started together, the curve of decline was similar to the curve of the basal metabolic rate obtained in cases in which thiouracil was given alone or where thyroxin was given after the basal metabolic rate had undergone a sustained fall (figure 8) In three cases that were started on the same date with the same treatment, except that two received thyroxin in addition to thiouracil, the thyroid glands of the two cases receiving combination treatment reverted toward a normal size more promptly and more completely than that of the control patient who received thiouracil alone

In four cases marked pitting edema developed during the first six weeks of treatment with thiouracil and cleared up without discontinuance of the drug The carbon dioxide combining power was found to be at the lower level of normal (50 to 54 volumes per cent), but was unaccompanied by any significant elevation of the serum chlorides or gross change in sodium and potassium values In one case extensive edema of the feet, legs, and hands occurred in the sixth week of treatment and after persisting for 12 days disappeared coincident with the giving of large doses of thiamin chloride One week later the patient was started on thyroxin and has had no recurrence of the edema The thyroxin was started after the edema had disappeared and thus had no part in the treatment in this particular case, but it has been noted that since the procedure of giving bicarbonate of soda, vitamin concentrates, and thyroid substance was adopted, no case of edema has been encountered This may be entirely coincidental, but the fact that edema developed only in cases not receiving thyroxin indicates that the water storage principle of the anterior pituitary hormone was unopposed by the diuretic action of thyroid hormone This hypothesis has received experimental confirmation from results obtained by Williams\* in an investigation of total body water in thyroidectomized rats

Three pregnant women with thyrotoxicosis (including series case 32) are receiving treatment Thiouracil was administered to one patient in her fourth month of gestation, after one month the basal metabolic rate had decreased from +59 to +30 per cent and the eye signs were diminishing, the effect on the child remains to be seen † In the case of A C (series case

\* In a study by Williams (Trans Assoc. Am. Physicians, 1941, lvi, 71, footnote) it was shown that total body water is increased in rats by thyroidectomy and increased in thyroidectomized rats by the administration of thyroid-stimulating hormone, and that the actions of thyroid-stimulating hormone and thyroid hormone on the total body water of such rats are antagonistic.

† Note added November 25, 1944 Thiouracil was discontinued in the ninth month of pregnancy because the basal metabolic rate was below +10 per cent Delivery was uncomplicated When examined at age five months the child was apparently normal and in good health The mother is in her fifth month of the puerperium and has not yet required the resumption of thiouracil treatment.

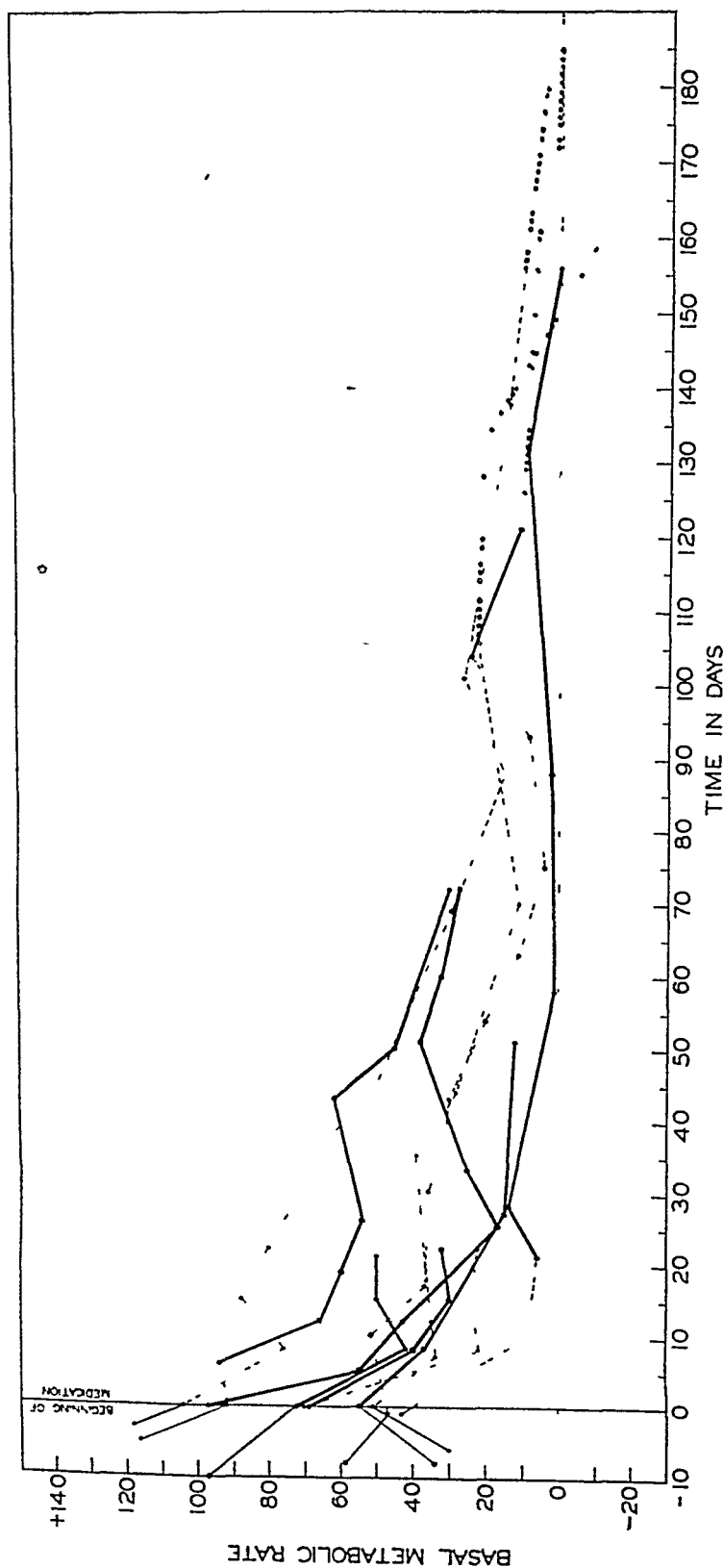


Fig 8 Comparison of results obtained from treatment of six cases of exophthalmic type with combined thioracil-thyroxine therapy (—) with results obtained from treatment of four cases without exophthalmos with thioracil only (---). The four cases were selected here because their initial basal metabolic rate determinations were roughly equivalent to those of the exophthalmic group. All medication discontinued (ooooooo). The dosage of thyroxine varied from 1/320 to 1/80 gr per day depending upon the severity of the eye signs.

32), treatment with thiouracil probably was not a causative factor in the abruptio placenta, but it should nevertheless not be disregarded. The patient was in the interval when the thiouracil had not begun to have its full effect, but she was no longer taking iodine. In the future a patient presenting a similar stormy history will be treated with thiouracil earlier in pregnancy and more sedation will be used until the thyroid hormone production is known to be very definitely inhibited.

In considering the safety of thiouracil medication it is relevant to mention one of the cases on which treatment was started after some hesitation. The patient was a 48-year-old colored female who was referred from the eye clinic because of severe exophthalmos and a basal metabolic rate of +97 per cent. In 1941 she had been admitted to the hospital because of left renal calculi and pyonephrosis. On sulfathiazole therapy she developed a severe persistent microcytic hypochromic anemia requiring numerous blood transfusions. One month after the anemia was brought under control, she underwent a nephrectomy for nephrolithiasis and pyonephrosis. In the past three years she has suffered from pyelonephritis and nephrolithiasis of the other kidney and from anemia. In using thiouracil for the treatment of this case the same precautions were observed as if the patient were on continuous sulfonamide therapy. Although she was known to be intolerant to sulfonamides, no untoward reaction to thiouracil was observed. An interesting side reaction in this case is that after receiving thiouracil-thyroxin therapy for three months, with progressive lowering of the basal metabolic rate but little change in the eyes, the patient suddenly presented herself one day in a state of alarm because her right eye had reverted to normal. The regression had taken place during the previous four days. The left eye continued to present the usual degree of proptosis.

## VI RESULTS OF TREATMENT

No case failed to respond to thiouracil. The higher the initial basal metabolic rate, the more rapid and dramatic was the response. In cases of cardiac decompensation due to latent hyperthyroidism or in mild toxic states, more thiouracil seems to be required to affect the pulse pressure and control the few thyrotoxic symptoms that may be present. In two cases of hypertension with poor renal function and moderately elevated basal metabolic rate (average +46 per cent), thiouracil after long treatment lowered the basal metabolic rate to +10 per cent but caused no change in physical findings such as tachycardia, increased pulse pressure, weakness, and tremor.

The average initial basal metabolic rate of the group which was given medical management exclusively was +60 per cent. In May of 1944, all of these patients were working and asymptomatic. They were returning for check-up visits at intervals ranging from a week to a month. Each survey included determinations of the basal metabolic rate, of cholesterol, and of non-protein nitrogen, complete blood counts, and urinalyses. (The

cholesterol determinations seem to be of little value in following the levels of hyperthyroidism )

Eight cases, including four of diffuse and four of nodular enlargement of the thyroid, were referred to surgery. The average pretreatment basal metabolic rate in these cases was  $+72$  per cent. The interval of pre-operative treatment was from 33 to 85 days. The operation and post-operative course were without incident in each case.

Nine of the first 22 cases developed transient leukopenia. In five of these cases the white blood cell count dropped to 3000, with less than 50 per cent polymorphonuclear cells, but in only one case did the cells show toxic changes. As soon as the white blood cell count reached 4000, the drug was discontinued for a minimum of 72 hours, the depressant effect was always transient and lasted usually about 48 hours. No depressant effect was noted after treatment with thiouracil had been resumed.

Microscopic hematuria and crystalluria developed in three cases before bicarbonate of soda was added to the routine.

Until recently no case of drug rash was encountered but series case 49, a 23-year-old colored female with initial basal metabolic rate of  $+94$  per cent, developed classical manifestations of pityriasis rosea in her third week of thiouracil treatment. Although this eruption is probably wholly unrelated to the medication with thiouracil, it represents the only approximation to a drug rash encountered in this series of cases. Treatment of this patient with thiouracil has not been discontinued. No case of drug fever has been encountered.

At the present time five patients who received thiouracil over a period of six months have received no medication for the past eight weeks, are still symptomless, and show no evidence of thyroid dysfunction. Two of these, C A (series case 2) and D M (series case 5), have already been discussed. A third case no longer requiring thiouracil is that of a 49-year-old woman who presented a combination of diffuse and nodular toxic goiter. Three years before her admission to the hospital, a diagnosis of colloid goiter had been made at another clinic. The basal metabolic rate at that time was  $+16$  per cent. Symptoms of toxicity developed later, and she was admitted to the hospital with a basal metabolic rate of  $+47$  per cent and early heart failure. In less than one month after treatment with thiouracil was begun, the basal metabolic rate had fallen to  $-6$  and  $-7$  per cent. For the next four months the patient was treated with 0.4–0.6 gm of thiouracil per day, for the following four months she was intermittently on a maintenance dose of 0.1–0.2 gm per day. During the second four-month period she was able to remain off the drug for intervals of two to three weeks, but occasional attacks of pharyngitis, tonsillitis, and arthritis, to which she was subject, caused temporary elevation of her thiouracil requirements. In May 1944, she was ending her second month of receiving no medication except vitamins, and the basal metabolic rate had remained at  $\pm 10$  per cent. The

diffuse thyroid enlargement had disappeared, but a large cystic nodule about 4 cm in diameter remained in the right side of the neck \*

The fourth case which no longer required thiouracil was that of a 35-year-old white female with a simple diffuse thyrotoxicosis that had responded to iodine with a fall in basal metabolic rate from +56 to +20 per cent in two months of active treatment and had remained fairly well controlled during the following year, but had then begun to present symptoms not relieved by iodine. The basal metabolic rate at the time of the second admission of this patient to the hospital was +67 per cent. She responded satisfactorily to thiouracil and phenobarbital. The former drug was discontinued completely after five months, but the patient was kept on phenobarbital ( $\frac{1}{4}$  gr four times a day). The last three determinations of the basal metabolic rate ranged between 0 and -5 per cent. The patient had taken no thiouracil for three months.

Five cases at the time of this report required 0.1 to 0.2 gm of thiouracil daily for maintenance of a basal metabolic rate of  $\pm 10$  per cent and control of symptoms. It seemed probable that their medication could be discontinued entirely within the next two months.

## VII DISCUSSION

Although there are several variations of the concept of the pituitary-thyroid axis, there is general acceptance of the principle of mutual checks and balances. The normal equilibrium and the abnormal variation which constitutes Graves' disease are expressed in figure 9 (taken from reference 9).

Knowledge of thyroid physiology is being increased by tracer studies with radioactive iodine. An understanding of the iodine metabolism makes possible an evaluation of the functional capacity of the thyroid, because iodine is the indispensable ingredient of thyroid hormone.

There is still some confusion as to the exact effect of thyrotropic hormone on the thyroid. Hertz and Roberts<sup>6</sup> concluded, after giving thyrotropic hormone to rabbits, that it causes an initial stimulation of the thyroid cells to collect iodine and, if sufficient iodine is available, there is involution and colloid storage, but that an excess of thyrotropic hormone in the presence of an iodine lack causes exhaustion of the thyroid with resultant loss of its capacity to collect iodine. Astwood and Bissell<sup>2</sup> have reported that injections of thyrotropic hormone cause hyperplasia of rat thyroids but that the glands contain an almost normal amount of iodine. On the other hand, they found that ablation of the hypophysis hinders the ability of the rat thyroid

\* This patient eventually came to operation for two reasons: the nodule in the right lobe caused some irritation by pressure on the trachea, without thiouracil for four months the patient became mildly toxic and began to lose weight.

The nine cases of Graves' disease that have had no evidence of thyrotoxicosis after receiving no medication for six months have been of the diffuse hyperplastic type. Thus far no nodular thyroid has had a remission of more than four months after treatment with thiouracil was discontinued.

to reaccumulate iodine after its store has been depleted. These investigators also found that injections of thyroxin produce an effect on the thyroid similar to that obtained by hypophysectomy. (Thus, it can be inferred that administration of thyroid hormone inhibits the production of thyrotropic hormone by the pituitary.) They concluded that whereas under certain conditions thyrotropic hormone promotes iodine uptake and storage by the thyroid, removal of this hormone hinders the ability of the gland to reaccumulate iodine after its depletion.

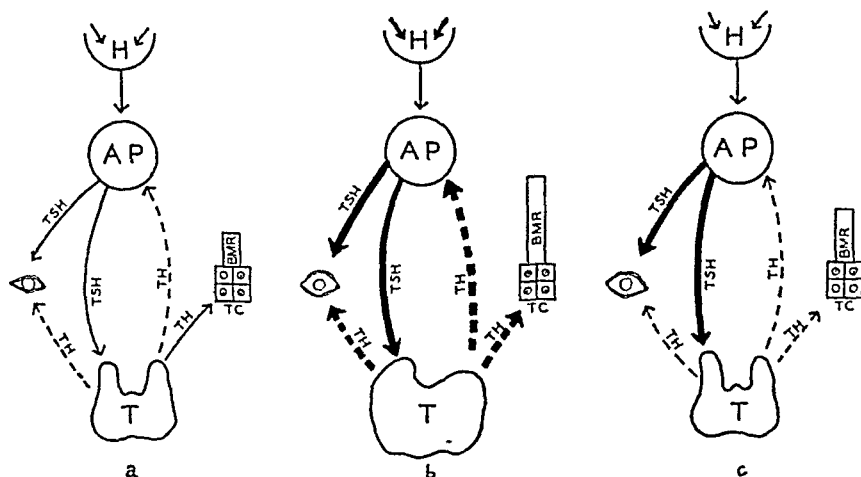


FIG 9 The pituitary-thyroid axis. (a) "In the normal individual Nervous influences impinge on the hypothalamus, H, which in turn stimulates the anterior pituitary, AP. The anterior pituitary stimulates the thyroid, T, humorally, by means of its hormone, TSH. The thyroid thus stimulated produces its hormone, TH, which stimulates tissue cells, TC, to increase their oxidative processes, BMR. Also TH inhibits AP, indicated by broken line, thus comes about the balance. A secondary effect is indicated upon the eye. TSH promotes exophthalmos, TH inhibits it" (Quoted from reference 9, p. 574).

(b) In Graves' disease with exophthalmos AP is stimulated to increased liberation of TSH by hypothalamic, cortical, or sympathico-adrenal influences. Increased TSH causes hyperfunction and hyperplasia of T. Without increased iodine supply the thyroid cannot respond to the increased TSH with sufficient TH to inhibit AP, thus it undergoes compensatory hyperplasia. It is possible that, although TH is increased in amount, it is iodine deficient and thus exerts its chief effect on the tissue cells with less effect on the pituitary and eye.

(c) In exophthalmos with moderate or no hyperthyroidism. The chief abnormal effect of TSH is on the eye. The effect of TH on AP is sufficiently inhibitory to maintain a relatively normal balance except for the oculotropic component.

Rawson, Tannheimer, and Peacock<sup>11</sup> have found that a thyroid treated with thiouracil takes up 10 per cent of radioactive iodine on the average, as compared with an average uptake of 56 per cent in control rat thyroids. A similar block to the synthesis and subsequent delivery of thyroid hormone has been found to be brought about by certain sulfonamides (sulfadiazine, etc.), as well as by thiouracil (see figure 10). Astwood and Bissell<sup>2</sup> reported that thyroid glands that had received both thiouracil and thyrotropin were found to have lost about half of their iodine content but still contained more iodine than glands treated with thiouracil alone.

From the above statements it can be concluded that suppression of thyrotropic hormone causes hyperplasia of the thyroid but impairs its ability to reaccumulate iodine after depletion. Thiouracil also causes a block to the uptake of iodine by the thyroid and thus its administration, concomitant with suppression of production of thyrotropic hormone by the administration of thyroxin, results in a reinforcement of the effect of each.

Studies of the mechanism of the action of thiouracil are still in progress. It is not known exactly how the thyroid is made refractory to iodine, but it is unlikely that thiouracil singles out the thyroid and acts directly upon it.

If thiouracil acts locally on the thyroid gland by setting up a block to the

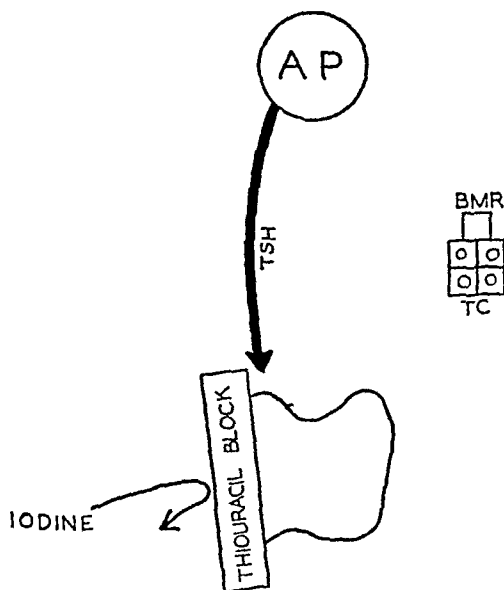


FIG 10 Diagrammatic representation of action of thiouracil on the thyroid. "Thiouracil causes an obstruction to the uptake of iodine. Again no active TH is put out and BMR falls. AP is stimulated by the absence of TH to produce an excess of TSH. Thyroid hyperplasia results, but in this case with no uptake of iodine." (Quoted from reference 11, p 252.)

intake of iodine, as suggested by Rawson, Tannheimer, and Peacock,<sup>11</sup> it would seem that after a time the gland would present a histological appearance identical with that of the thyroid of simple iodine deficiency, however, a thiouracil-treated thyroid, though presenting a variable appearance, has little resemblance to the thyroid of simple iodine deficiency (figure 11b).

If the action of thiouracil is considered to be mainly a local one on the thyroid, all thyroids removed after preoperative medication with this substance would be expected to bear some resemblance to one another. However, it has been found that thiouracil-treated thyroids may present any histological appearance from hyperplastic exhaustion to complete involution.

If thiouracil causes a local block in the thyroid to the synthesis and deliv-

ery of thyroid hormone, it would seem likely that the feeling of normality experienced by the patients would ensue subsequent to this decreased hormone level. However, it has been found consistently that the feeling of well-being and the generally improved appearance have occurred before there was any significant decrease in the basal metabolic rate.

Suppose that thiouracil were a tissue cell depressant rather than primarily a thyrotropic substance, then the above aspects, which seem to be discrepancies, can be brought into harmony with the general pattern. It has been reported<sup>15</sup> that when thiouracil is given by mouth to human beings, its concentrations are greatest in the bone marrow, the adrenals, and the pituitary. On the supposition that as a tissue cell depressant thiouracil exerts its effect first on the most delicate structures, i.e., tissues in which there is a constantly shifting dynamic equilibrium as in the pituitary and adrenals, its action may be represented as shown in figure 12a.

Recent investigations on rats have revealed that after the thiouracil effect has been obtained, if thyroxin is given (or the pituitary is removed), there is a reaccumulation of densely staining colloid material of low iodine content.<sup>2</sup> The colloid formed under these conditions has shown abnormal fluorescence—a further evidence of its low hormone content (figure 11c).<sup>4</sup>

Contrary to what was expected from the animal experiments of Astwood and others, who found the goitrogenic action of thiourea derivatives and of sulfonamides to be prevented by thyroxin or desiccated thyroid, no case in this series that received combined treatment presented any evidence of refractoriness to the effect of thiouracil in lowering the basal metabolic rate (figure 8). All cases with exophthalmos or significant eye signs and certain recent non-ophthalmic cases have received thyroxin from the beginning of treatment and have presented no signs of incompatibility or antagonism. On the contrary, there has been noted a tendency toward a more rapid return to normal, both subjectively and objectively, with less cyclic fluctuations than if treatment were with thiouracil alone.

The dose of thyroxin sufficient to achieve favorable results is small. Frequently, during the first two weeks of medication with thiouracil alone, there have been transient manifestations of ocular irritation, such as burning, lacrimation, and conjunctival hyperemia. These have disappeared within 24 hours after receiving two to four doses of thyroxin (1/160 gr.). These eye signs have been noted very infrequently in patients receiving thyroxin from the beginning of treatment.

Transient enlargement of the thyroid has been noted in some cases during the first two weeks of treatment with thiouracil. Whether this is due to compensation on the part of a previously overstimulated, active gland suddenly deprived of its secretory stimulation or to some other cause, administration of thyroxin seems to inhibit such hyperplasia. However, the possibility of an entirely different mechanism may be suspected from an incident involving one patient with exophthalmos who had been discharged from



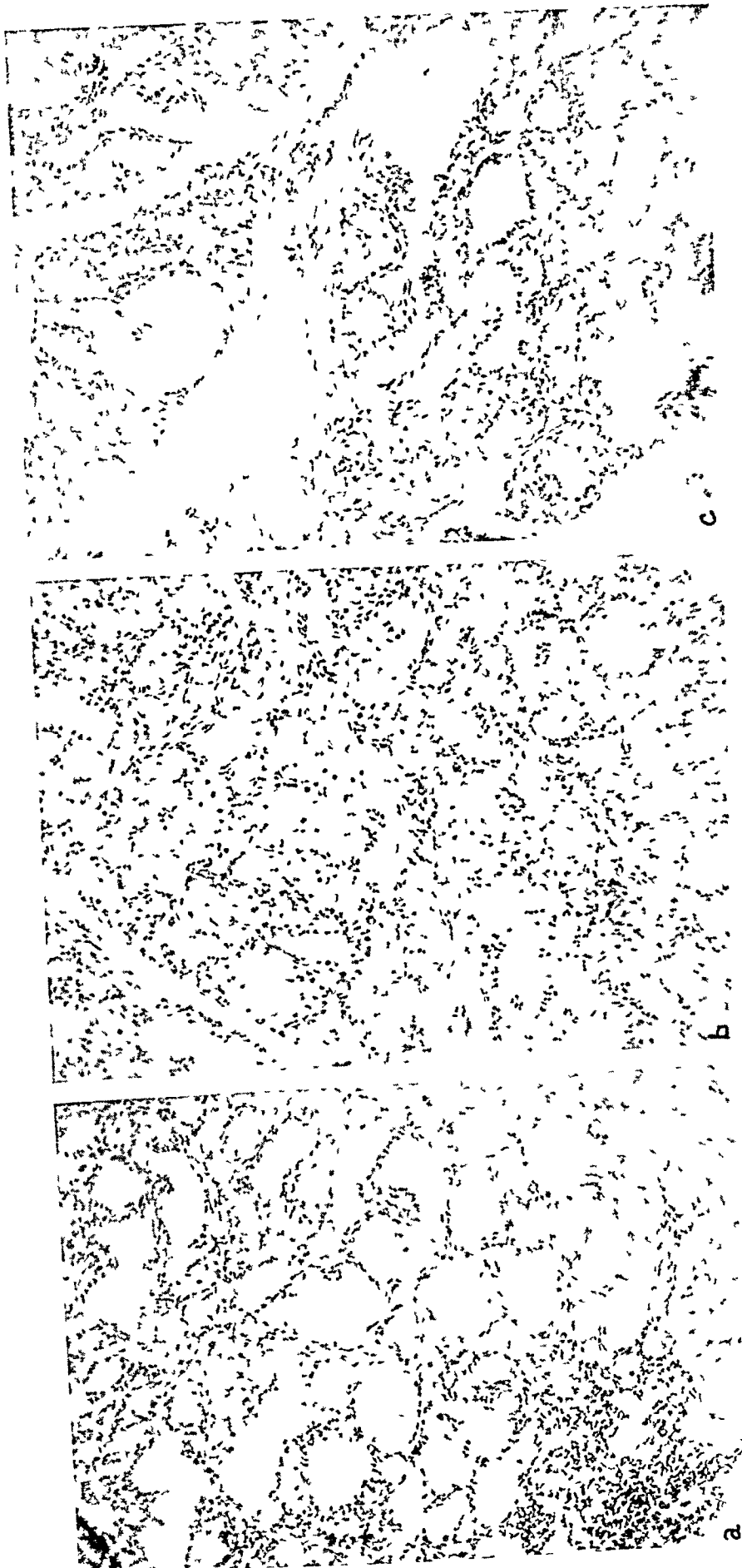


Fig 11 (a) Biopsy of a hyperplastic thyroid of a patient with a basal metabolic rate of +84 per cent before treatment was instituted The gland shows (b) Same gland removed at operation after 75 days of treatment on thouracil Basal metabolic rate at time of operation was +30 per cent no decrease in lymphoid or epithelial hyperplasia, no decrease in vascularity, and no increase in colloid content Average pre-treatment basal metabolic rate was +66 per cent (c) Gland removed at operation when basal metabolic rate was +19 per cent after 25 days of combined thouracil-thyroxin treatment A slight decrease in vascularity and hyperplasia can be noted

the hospital after one month of combined thiouracil-thyroxin therapy with a reduction in the basal metabolic rate from  $+59$  to  $+38$  per cent and improvement in the degree of exophthalmos. One week later she returned with her pretreatment degree of exophthalmos and a thyroid enlarged to a size greater than the maximum found previously. It was discovered that instead of taking 0.4 gm of thiouracil and  $1/80$  gr of thyroxin daily, she had been taking an equivalent of 0.2 gm of thiouracil and  $1/20$  gr of thyroxin. The basal metabolic rate was found to be still  $+38$  per cent and there were no other ill effects. One week later, after receiving 0.4 gm

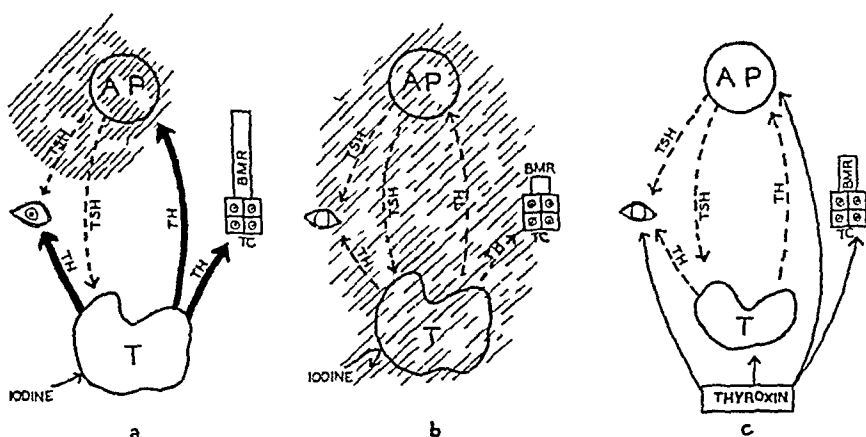


FIG 12 (a) Graves' disease with beginning thiouracil treatment AP is inhibited, thus there is decreased production of TSH. The thyroid is still putting out excess TH and thus is becoming rapidly depleted of iodine. With TSH inhibited, there is less stimulus to secretion and the thyroid may undergo transiently a hyperplasia compensatory to the lack of secretory stimulation. The TH that is still being elaborated from the thyroid reserve enjoys an unopposed diuretic action on the eye and an inhibitory action on AP. The shaded area represents the depressant action of thiouracil.

(b) Graves' disease with full thiouracil effect. Concomitant with its depressant action on AP, which results in a lowering of the amount of TSH, thiouracil exerts a depressant action on the thyroid by interfering with the iodination of the thyroglobulin molecule<sup>2</sup> and thus preventing the elaboration of any physiologically active hormone. The shaded area represents the depressant action of thiouracil.

(c) Graves' disease treated with thiouracil and thyroxin. The pituitary-thyroid equilibrium is now established but is depressed toward a resting phase. Small doses of thyroxin have an unopposed effect on AP, particularly on its oculotropic component, and also, to some extent, on TC. The thyroid becomes smaller and fills with inert colloid.

of thiouracil daily without thyroxin, the gland was found to be of normal size and the eyes were improved. The basal metabolic rate was  $+18$  per cent, notwithstanding the fact that the patient had been married the evening before. From this one case it would seem that when thyroxin is given in large amounts after the thyroid has reacted to thiouracil, it not only fails to inhibit hyperplasia but stimulates the thyroid to a marked increase in size without, however, exerting any particular calorogenic action.

To sum up, from animal experiments it is concluded that thiouracil exerts an effect on the thyroid similar to that obtained by hypophysectomy or by suppression of pituitary function by giving thyroxin. The effect con-

sists principally in a refractoriness to the uptake of iodine and to the consequent synthesis in the gland of effective thyroid hormone. There is no reason to doubt that the mechanism is similar in man. The administration of thyroxin enhances the action of the thiouracil by further inhibiting the production of thyroid stimulating hormone and at the same time furnishes effective thyroid hormone to meet the requirements of other important end organs such as the eye and the tissue cells.

### VIII SUMMARY AND CONCLUSIONS

It is probable that the state of toxic hyperthyroidism is a condition of generalized imbalance in which the thyroid plays a secondary contributing part. Because the gland is not the primary source of the pathological disturbance, the beneficial results of thyroidectomy must be brought about through establishing a temporary block and thus breaking a vicious circle. If thiouracil or a similar thiourea derivative can safely inhibit the formation of or inactivate the effect of thyroid hormone, the same end results should be obtained as in cases undergoing thyroidectomy. The risks of the two procedures—medical and surgical—remain to be evaluated by more cases treated over a longer period of time.

In the series of 50 cases treated with thiouracil at the University Hospital, no serious complications were encountered during a period extending from one to 10 months. No case of drug intolerance, idiosyncrasy, or refractoriness was found. Thus far leukopenia has been the only serious effect and this has been transient, however, unless frequent blood examinations are made, this might represent an early step in the development of agranulocytosis. The depressant effect of the drug on the hematopoietic system must be anticipated throughout the course of treatment.

No case failed to respond to the drug, but some responded more satisfactorily than others. In general, the higher the initial basal metabolic rate, the more dramatic was the response (figure 8). All cases improved first subjectively and then objectively. The effect of vitamins, sedation, and rest has been partially evaluated, at present it is believed that such adjunctive measures enhance the efficiency of thiouracil but have little intrinsic curative properties.

No case has required operation, although planned elective thyroidectomy has been considered feasible in certain instances because of economy, convenience, or cosmetic reasons. The patient coming to operation is treated in the same manner as one with simple colloid goiter, with the exception that measures are taken to control the greater vascularity encountered in a thyroid treated with thiouracil. Postoperatively, sodium sulfadiazine is given parenterally if there is any atelectasis, significant elevation of temperature, or sign of incipient thyroid storm. There have been no post-operative complications referable to treatment with thiouracil.

Microscopic sections of thyroid glands treated with thiouracil have ex-

hibited varying degrees of hyperplasia and colloid content. It is believed that the thiouracil effect is brought about by depression of normal enzyme reactions of tissues in general but especially of the pituitary (leading to suppression of synthesis of thyroid stimulating hormone) and of the thyroid (leading to inhibition of iodine uptake). Less hyperplasia and more colloid have been noted in sections of two glands treated with thiouracil and thyroxin. Sections of two glands treated with thiouracil and iodine were in every way similar to thyroids treated with thiouracil alone.

Over half of the 50 cases have received from 1 gr. of desiccated thyroid to 1/80 gr. of thyroxin daily, the dose being dependent on the degree of exophthalmos present. In no case did the thiouracil effect appear to be inhibited by giving thyroid substance. It has been found that there is a trend toward a state of normal endocrine balance on thiouracil therapy alone, but the restoration is brought about more quickly, more completely, and with less frequent unpleasant side reactions when thyroid substance is given in combination with thiouracil.

Four cases which have been observed for the past eight months have required no medication of any sort for the past three months and as yet appear to be in a state of normal physiologic equilibrium with basal metabolic rates in the range of  $\pm 12$  per cent. Those patients who have relapsed because treatment was discontinued too soon or because of intercurrent infection or emotional stress, have reacted in the same manner as have patients who have developed recurrent hyperthyroidism following thyroidectomy. Such patients have responded as satisfactorily to the second round of medication with thiouracil and thyroxin as they did at the beginning of treatment.

Because of the cyclic nature of Graves' disease the remissions obtained by any treatment must not be confused with "cures" except in that small group of patients who have fallen victims to the malady because of a definite etiologic factor which can be removed.

The author wishes to thank the Department of Pathology of the University Hospital for the preparation of the histopathological specimens reproduced in this paper.

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# USE OF THIOURACIL IN THE PREOPERATIVE PREPARATION OF PATIENTS WITH SEVERE HYPERTHYROIDISM<sup>1</sup>

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A PRELIMINARY report on the use of thiouracil in the preoperative management of 12 toxic hyperthyroid patients at the Lahey Clinic was published in May 1944<sup>1</sup>. We were convinced of the effectiveness of this drug and since then we have continued to use thiouracil as a preoperative therapeutic agent in a total of 64 patients. The patients treated were severely toxic and would have incurred more than the average surgical risk if they had been prepared in the usual manner by administration of Lugol's solution. Most of these patients would have required multiple stage operations, but with thiouracil most went through a subtotal thyroidectomy safely and with no reaction.

Our observations on this group were as follows. There were 51 females and 13 males with both types of hyperthyroidism—50 patients had primary hyperthyroidism or exophthalmic goiter and 14 patients had adenomatous goiter with hyperthyroidism. The ages varied from 11 years (a girl with severe, exophthalmic goiter) to 72 years. The average age was 43 years, 27 patients were over 50 years of age. The duration of the hyperthyroidism ranged from three months to 15 years. Twenty-nine patients had had the disease for over two years, of these, 15 had been ill more than four years. The average weight loss of the group was 29 pounds, with a loss of as much as 98 pounds in one case. The initial basal metabolic rate varied from +21 per cent to +98 per cent, the average rate being +51 per cent. These patients were all considered to have severe hyperthyroidism because of their being in the older age group, because they had had the disease for a long time and had high basal metabolic rates. Fifteen patients with adenomatous goiter were classified as thyrocardiacs, having either heart failure or auricular fibrillation without heart failure.

## PLAN OF TREATMENT

Our early experience quickly taught us that when thiouracil<sup>†</sup> is used the maximum improvement must be strived for, in other words, patients should not be sent to operation until a normal or nearly normal basal metabolic rate is recorded. The objection to partial control is illustrated by two patients (figures 1 and 2) who were sent for operation, the first patient after

\* Received for publication December 12, 1944.

† The thiouracil was supplied by Dr. B. W. Carey, Lederle Laboratories, Inc., Pearl River, New York.

20 days of thiouracil with the basal rate of  $+26$  (previous rate,  $+60$ ) and the second patient after 40 days of treatment with the basal rate of  $+44$  (previous rate,  $+60$ ). In both patients the operative course was so unsatisfactory that only a hemithyroidectomy was done. The fact that both patients had a severe postoperative reaction indicated that the decision of the anesthetist and surgeon to limit the operation to a hemithyroidectomy was justified. As a result we now continue the daily administration of 0.6 gm of thiouracil until the basal metabolic rate is practically normal and hyperthyroid symptoms have subsided. The time required to accomplish this

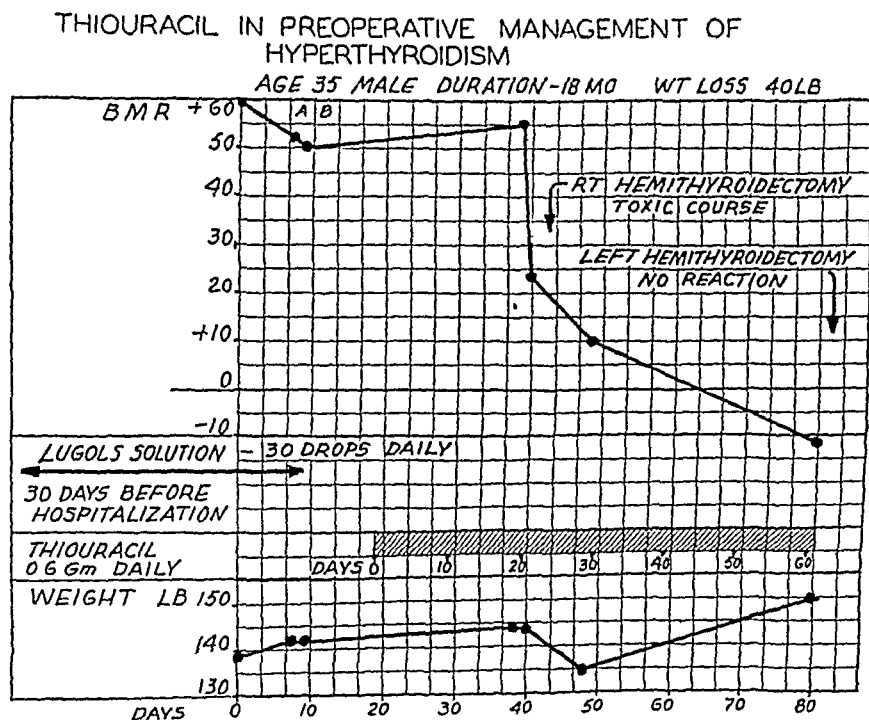


FIG 1 Case of severe hyperthyroidism, showing slow response to thiouracil because of previous iodine medication. Operation was done before maximum improvement was obtained.

degree of improvement is determined by the height of the basal metabolic rate. Actually, it has been found that approximately one day of treatment with thiouracil is required for each per cent of elevation in the basal rate. Those patients who had received Lugol's solution before the administration of thiouracil responded less quickly and usually required a slightly longer time for treatment. With this knowledge, the date of their readiness for operation can be predicted and hospital arrangements can be made in advance.

The 64 patients had an average basal rate of  $+51$  per cent and after undergoing treatment for an average period of 58 days, the basal rate was  $+8$  per cent (figure 3). The size of the gland did not seem to have any

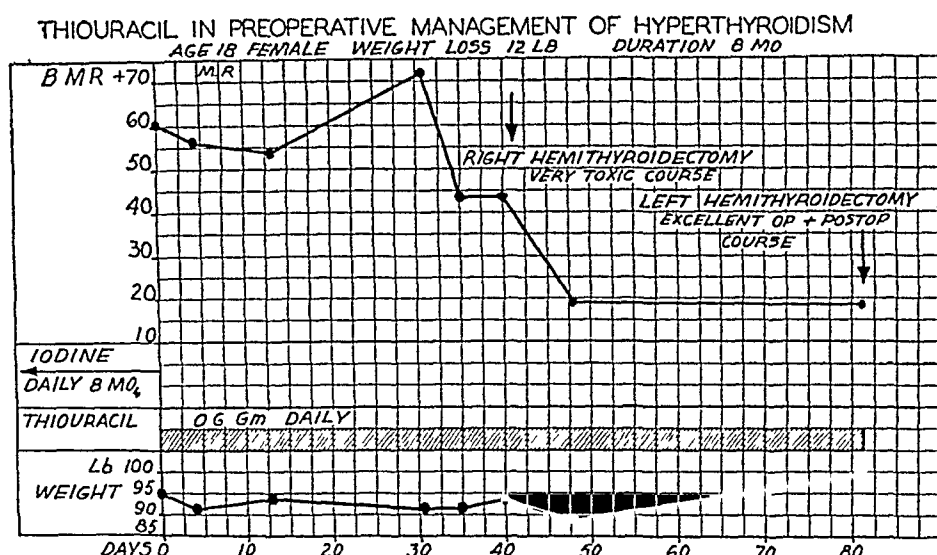


FIG 2 Case of severe hyperthyroidism, showing slow response to thiouracil because of previous iodine treatment. Operation was done before maximum improvement was obtained.

decided relationship to the duration of treatment. Associated with subjective improvement there was an average gain in weight of 13 pounds. The greatest gain in weight was 30 pounds, and 13 patients gained more than 20 pounds.

Treatment of those patients who did not have heart failure was carried

#### THIOURACIL IN PREOPERATIVE TREATMENT OF SEVERE HYPERTHYROIDISM

##### RESPONSE IN 64 CASES

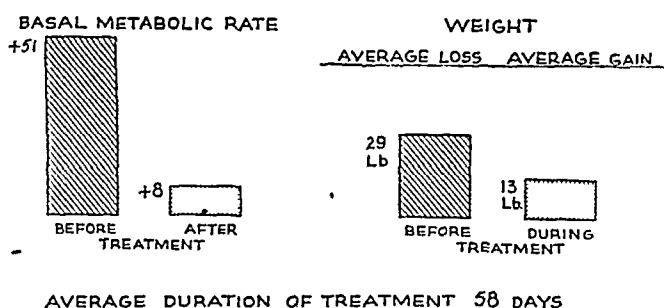


FIG 3 Drop in basal metabolic rate and gain in weight with thiouracil treatment are shown.

on at home, the patients returning to the Clinic every two or three weeks for routine examination and differential white blood cell counts. Patients were advised to rest and eat a full diet, with lunches between meals. Patients with heart failure were hospitalized and as soon as cardiac compensation was established they were sent home on ambulatory treatment.



## OPERATIVE PROCEDURES

Fifty-two patients were subjected to subtotal thyroidectomy, 12 patients to hemithyroidectomy. Of the latter 12 patients, four had very large goiters and it was thought at the time unwise to do a subtotal thyroidectomy. This occurred early in our experience with thiouracil and before we had learned about smooth anesthesia and postoperative course of thiouracil-treated patients (figure 4). Speed is no longer a factor, since postoperative reactions do not occur, and now extremely large glands are removed at one stage (figure 5). Four patients were not treated long enough with thiouracil to permit subtotal thyroidectomy without risk. Four patients were prepared for second stage operations with thiouracil after having had a first stage procedure performed following iodine preparation because their con-

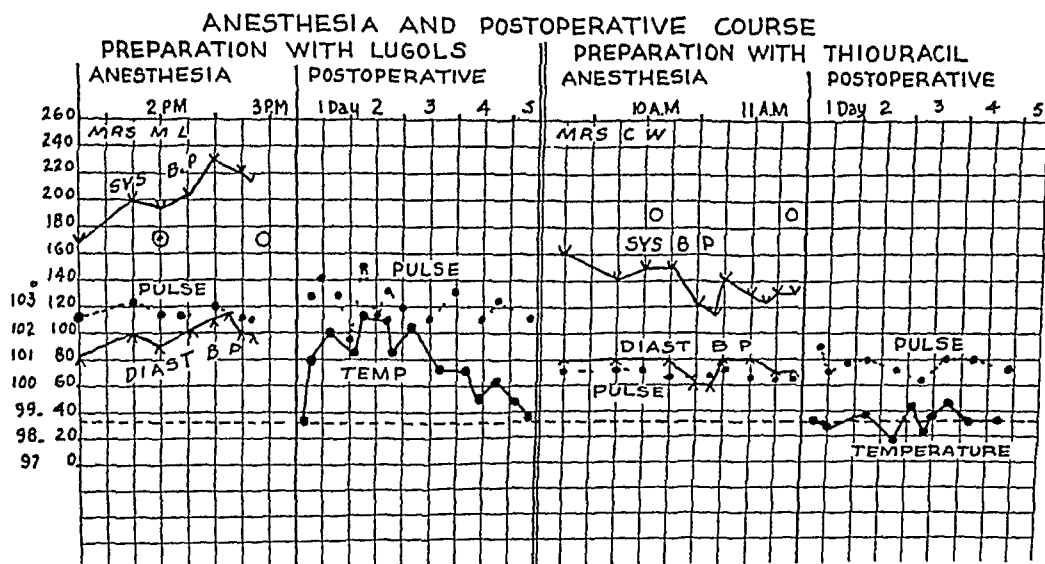


FIG 4 Comparison of anesthesia and postoperative course following administration of Lugol's solution and of thiouracil

dition after the first operation was thought to be too serious to warrant a second stage procedure without considerable risk. Thus treated, they had an uneventful anesthesia and postoperative course.

When the first patients receiving thiouracil underwent thyroidectomy, a most unsatisfactory surgical complication was encountered. The gland was found to be soft and friable, and bleeding was so extensive that there was difficulty in carrying out the usual surgical technic, including the isolation of the parathyroid glands and the recurrent laryngeal nerve. Some of our surgeons disliked operating on these patients for this reason. The difficulty was overcome when Lugol's solution was administered along with thiouracil (figure 6). Thiouracil is given until the basal metabolic rate approaches + 20 per cent, when iodine is started. It is continued for three weeks pre-

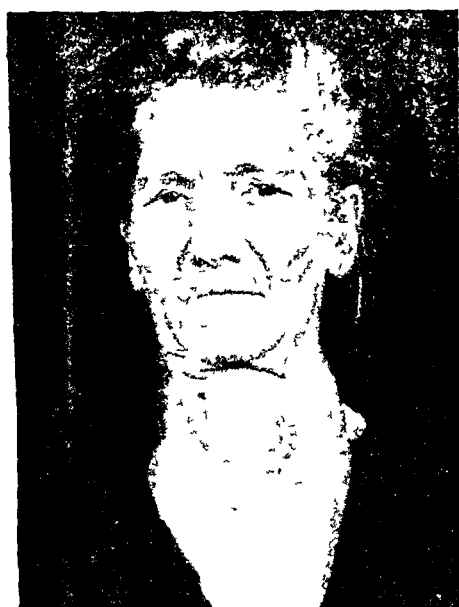
operatively, discontinuing the thiouracil one week before operation. This method produced a satisfactory state of involution as determined at operation and by microscopic examination of excised thyroid tissue in all cases except one.

Further studies probably will show that iodine is not required preoperatively in patients with adenomatous goiters or in patients with long-

Adenomatous Goiter with Hyperthyroidism, Preoperative Treatment  
with Thiouracil

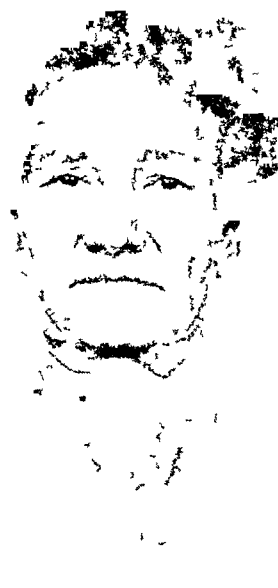
Duration of Disease 6 Years

Weight Loss 98 Pounds, Age 60



July 13, 1944

B M R + 63  
Weight 110 lb  
Pulse 112



October 10, 1944

(89 Days)

+ 21  
133 lb  
88

FIG 5 Severe hyperthyroidism caused by adenomatous goiter, showing clinical response to thiouracil. Subtotal thyroidectomy was done in one stage.

standing primary hyperthyroidism. In the former the gland remains firm, and in the latter spontaneous involution over the years is sufficient to prevent the gland from bleeding excessively.

#### TOXIC REACTIONS OF THIOURACIL

Toxic manifestations developed in eight cases,\* only one of which is included in the above operated group. This patient had reached a suf-

\* Eight of a total of 119 patients who were given thiouracil.

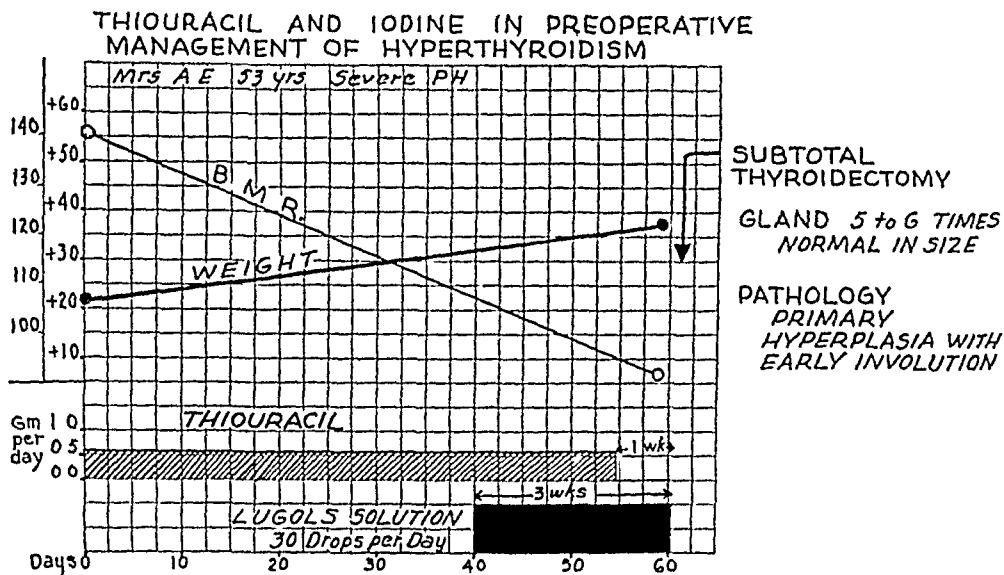


FIG. 6 Plan of combination of thioracil and Lugol's solution which produces satisfactory involution in the thyroid gland at operation

ficiently satisfactory condition to enable a subtotal thyroidectomy to be done. Iodine was employed for preoperative preparation of the remaining patients. The reactions consisted of (a) skin eruption, one patient, (b) fever reaction, four patients, (c) leukopenia, three patients. The skin eruption was generalized, being macular papular in type and quite pruritic. Relief was obtained immediately on stopping treatment.

Fever reactions occurred within the first 10 days of treatment (figure 7). The temperature ranged to 102 or 103° F, and was associated with generalized aches and pains. It returned to normal when thiouracil was dis-

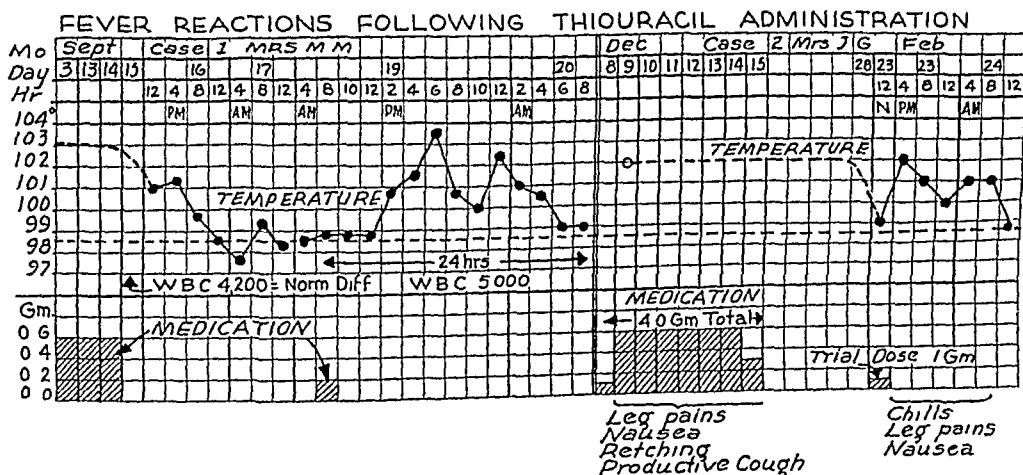


FIG 7 Fever reaction with thiouracil, showing immediate return of fever when small dose is given again

TABLE  
Blood Changes under Treatment with Thiouracil

Date		Hgb %	W B C count	Differential Count					
				Poly-morphonuclears	Band forms	Lymphocytes	Mono cytes	Eosinophils	Basophiles
<i>Case 1</i> 6-14-43			5,900						
5- 9-44	Thiouracil started, 0.3 gm a day								
7-12-44	Sore throat began on 7-13		2,400	36		54			
7-14-44	Drug stopped								
7-17-44			4,300	29		46			
8- 8-44			4,550	54		33			
<i>Case 2</i> 12-11-43	Thiouracil started, 0.6 gm a day for 1 wk, then 0.3 gm a day								
1- 8-44			7,500	48		42	9.5		0.5
2- 5-44	Cut to 0.1 gm a day								
3-18-44	Cut to 0.6 gm a wk		7,800	59		32	12.5		
7- 1-44	Drug stopped	106	1,900	8	6	33	3		1
(50 cells counted)									
7- 6-44		99	2,850	34	4	57	5		
7-15-44		101	6,400	55	0	38	7		
<i>Case 3</i> 11- 2-43		113	9,250	66	1	24	8	1	0
11- 3-43	Thiouracil started, 0.6 gm a day								
11-13-43	0.4 gm a day								
12- 4-43	0.2 gm a day								
1- 3-44	0.1 gm a day		8,600						
2-14-44	0.1 gm every other day		9,700						
8-12-44	Drug stopped		3,800 4,800	23	0	63	14	0	0
9-14-44			7,200	53		39	5	0	0

continued, and in all cases a repeated small dose of thiouracil caused an immediate return of fever

Leukopenia occurred after two months, eight months, and 10 months of treatment in three cases, the dose being 0.3, 0.1 and 0.5 gm daily. Usually the change was sudden, with reduction in the total number of white cells and in the polymorphonuclear cells. A return of the blood to normal quickly followed discontinuance of the drug (table). One patient presented the early stages of agnucleocytic angina. Fortunately, it was recognized early and the drug was stopped. These changes make blood examinations essential during the administration of thiouracil.

The economic advantage of thiouracil can be realized when it is known that the hospital stay now is seven to 10 days as compared with weeks when patients with severe hyperthyroidism were prepared with Lugol's solution.

### SUMMARY

Further experience with the use of thiouracil confirms our early impression that this drug is extremely valuable in the preoperative management of patients with severe primary hyperthyroidism or adenomatous goiter with secondary hyperthyroidism.

Thiouracil should be administered until maximum benefit is obtained, and at that time operation can then be carried out without risk.

The technical difficulties at operation which occurred in patients treated only with thiouracil have now been overcome by the added use of Lugol's solution during a three-week period immediately before operation.

The value of thiouracil lies in the reduction of the risk of surgical treatment which we believe is still needed to terminate hyperthyroidism with greater certainty and greater safety.

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# INTERCAPILLARY GLOMERULOSCLEROSIS <sup>1</sup>

By IRVING I. GOODOR, M.D., *Boston, Massachusetts*

IN 1936, Kimmelstiel and Wilson <sup>1</sup> first described a pathologic change in the kidneys which they called intercapillary glomerulosclerosis. Of their eight cases, seven were known to have had diabetes mellitus. Since that time there have been several conflicting reports regarding the incidence and nature of this lesion. This study was undertaken in an attempt to correlate the glomerular changes with various clinical and anatomic findings in the hope that some light may be thrown on the pathogenesis and significance of the lesion.

In the eight instances of intercapillary glomerulosclerosis reported by Kimmelstiel and Wilson, diabetes mellitus, hypertension, albuminuria, and edema were present. Anson <sup>2</sup> in 1938, and Newburger and Peters <sup>3</sup> in 1939 added several cases, and, in general, agreed with the observations of Kimmelstiel and Wilson. In 1941, Siegal and Allen <sup>4</sup> and Allen <sup>5</sup> investigated the clinical and pathologic aspects of the condition. These investigators noted that the lesion occurred in 35 of 105 diabetic patients, and in only one of 100 non-diabetic patients with hypertension. The complete renal syndrome including albuminuria, edema, hypertension, and uremia occurred in only three of 10 patients with advanced intercapillary glomerulosclerosis. Allen studied the kidneys anatomically and concluded that the lesion is actually a focal intramural glomerulosclerosis, rather than intercapillary, as it had previously been considered. He found, also, that hyalinization of the islands of Langerhans occurred as frequently and to as great a degree in the pancreases of diabetic patients without intercapillary glomerulosclerosis as in those with it.

In 1942, Horn and Smetana <sup>6</sup> published a review of all instances of diabetes mellitus and of arteriolar nephrosclerosis in the autopsy files of the Presbyterian Hospital in New York since 1909. Of 144 patients with diabetes mellitus, 22.9 per cent showed intercapillary glomerulosclerosis. Of 126 instances of arteriolar nephrosclerosis without diabetes, 25.4 per cent showed the glomerular lesion. They stated, however, that advanced lesions occurred only in diabetic patients.

## MATERIAL

A history of clinically-manifest diabetes mellitus was recorded in 214 of 10,000 consecutive autopsies performed at Washington University School of Medicine from 1910-1942. Since many of these patients had no records of glucose tolerance tests, the diagnosis of diabetes mellitus was accepted in

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the presence of elevated levels of sugar in the blood in the fasting state or extremely high non-fasting levels in the absence of administration of glucose intravenously. The clinical history and autopsy protocol of each case were reviewed, and all relevant observations charted. In addition, microscopic sections of the kidneys and pancreas of each case were studied. In all cases showing evidence of intercapillary glomerulosclerosis or of hyalinization of the islands of Langerhans additional sections were prepared and stained with Heidenhain's aniline blue.

Several series of controls were selected. One of these included 214 cases of patients without diabetes mellitus, as determined by the absence of glucose in the urine and a blood sugar level below 120 mg per 100 cc. Half of these patients had hypertension, the systolic pressure being greater than 150 mm of mercury or the diastolic greater than 100 mm. This group of 214 cases was chosen so that the ages corresponded with those of the test series, and also so that they were spread over the 32 year period in the same way as were the diabetic patients.

Another control series was selected, composed of 100 consecutive non-diabetic patients in whom the kidneys showed arteriolar disease. To study the part played by age in the development of intercapillary glomerulosclerosis, 50 cases of non-diabetic patients over 70 years of age were examined, and a similar number from five to 20 years of age.

### ANATOMIC OBSERVATIONS

Intercapillary glomerulosclerosis is recognized by the presence of dense hyaline material located in the glomeruli between capillary loops. It is most commonly present near the periphery of the glomerular tuft, and in many instances is associated with advanced thickening of the wall of the afferent arteriole. Occasionally the focal masses of hyaline material are present at many points in the glomeruli, and, indeed, when large enough a single mass may occupy over half the volume of the glomerulus. The lesion is diffuse in most instances, and if the condition is present to any extent it is common for most of the glomeruli to be involved in some degree. Thus, in grading the severity of the disease, the number of glomeruli involved is unsatisfactory as an index. It would appear to be more reliable to consider the relative amount of hyaline material in each mass, and the extent of involvement of the individual glomeruli. In this study a lesion is considered of slight degree when there are no large hyaline masses and the glomeruli contain only small deposits of material between the capillary loops. These deposits are most commonly located at the periphery of the glomerulus, but are occasionally noted elsewhere (figure 1). A lesion of advanced grade is one in which almost every glomerulus contains one or more large hyaline masses (figure 2). The remainder are considered lesions of moderate degree (figure 3).

*Incidence of the Lesion* Of the 214 diabetic patients, the kidneys of 94

(44 per cent) showed the lesion of intercapillary glomerulosclerosis in varying degree. Twenty of these were of advanced grade, 25 were of moderate severity, and 49 were slight.

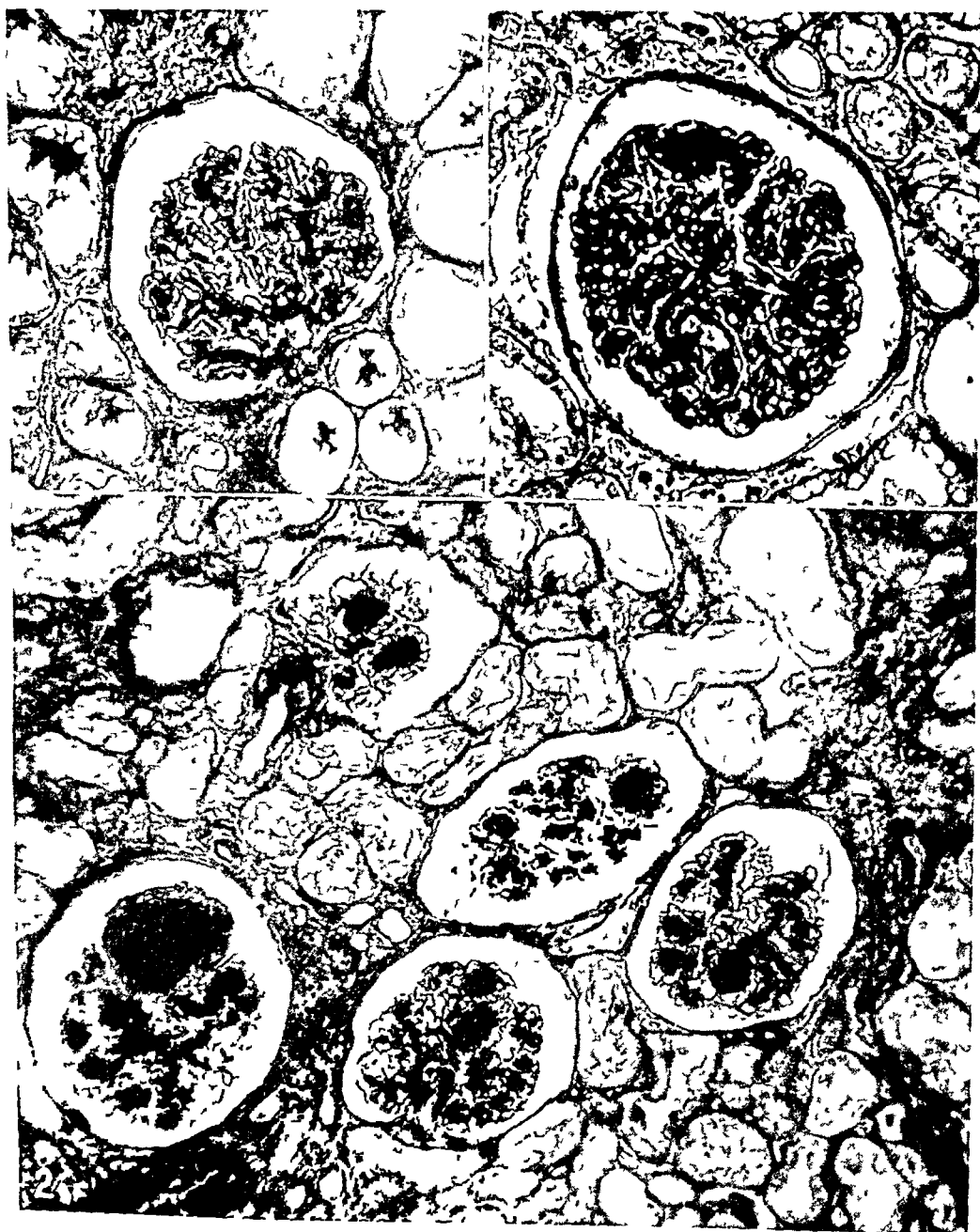


FIG 1 A mild lesion of intercapillary glomerulosclerosis. There are several small foci of hyaline material between the capillary loops ( $\times 108$ ).  
FIG 2 An advanced grade of intercapillary glomerulosclerosis. All of the glomeruli in the section contain large masses of hyaline material ( $\times 108$ ).  
FIG 3 A moderate grade of intercapillary glomerulosclerosis. Many glomeruli in the section contain masses of hyaline material of moderate size ( $\times 135$ ).



*Relation to Hyalinization of Islands* Hyalinization of the islands of Langerhans was found in 71 (33 per cent) of the 214 cases of diabetes mellitus. Of these, 46 (64 per cent) were associated with intercapillary glomerulosclerosis. Of the 94 instances in which the renal lesion was found, 48 (51 per cent) also showed hyaline change in the islands of Langerhans (figure 4).

These figures are higher than those of Siegal and Allen,<sup>1</sup> who found intercapillary glomerulosclerosis in 33.3 per cent of 105 diabetic patients over 40 years of age. These authors reported that about half of those cases with hyaline islands also had the glomerular lesion. In our series, 64 per cent of

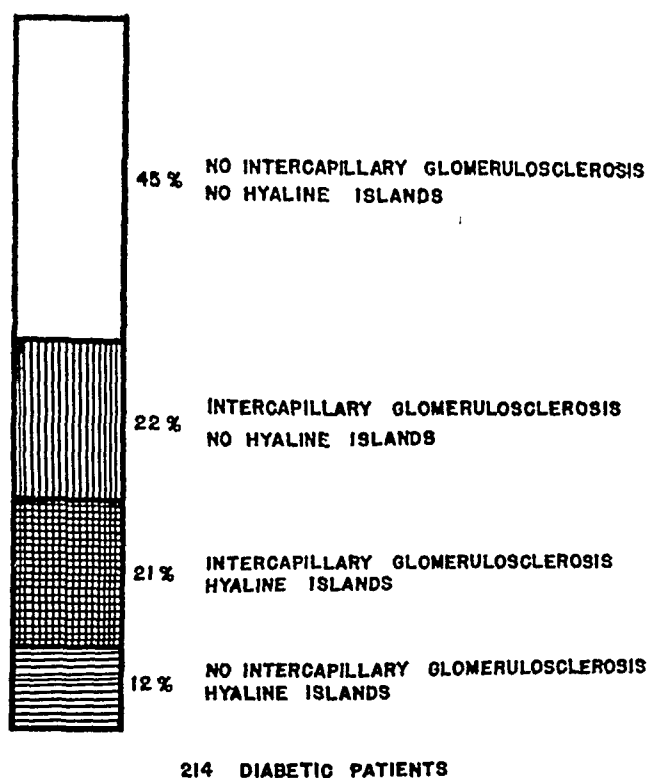


FIG 4 A chart to show the relative and combined incidence of intercapillary glomerulosclerosis and hyalinization of the islands of Langerhans in 214 diabetic patients

the cases with hyaline islands also had intercapillary glomerulosclerosis. Although this figure might lead one to suspect that there is a relation between hyaline islands and intercapillary glomerulosclerosis, the fact that only 51 per cent of the cases with the renal lesion were associated with hyalinization of the islands of Langerhans points in the opposite direction. Of 49 patients with a slight degree of intercapillary glomerulosclerosis, 24 (49 per cent) had hyalinization of the islands of Langerhans. Hyalinization of the islands was present in 13 (52 per cent) of patients with moderate renal lesions, and in nine (45 per cent) of patients with advanced lesions.

*Relation to Age* The incidence of hyalinization of the islands of Langerhans in diabetic patients increases with advancing age, whereas the incidence of the glomerular lesion reaches a plateau between 30 and 40 years of age. There is a rise in the incidence of intercapillary glomerulosclerosis after the age of 70 years (figure 5). Fourteen patients, or 15 per cent, of the group with intercapillary glomerulosclerosis were under 40 years of age. Two female patients, 17 and 19 years of age, respectively, neither of whom had received insulin, showed the lesion in the kidneys. The lesion was also present in slight or moderate grade in three patients dying in the third decade. The age incidence of intercapillary glomerulosclerosis in our series thus differs from the findings of other investigators in that the youngest patient thus far reported to have shown this lesion was 35 years of age. In our control series, intercapillary glomerulosclerosis was not found in the kidneys

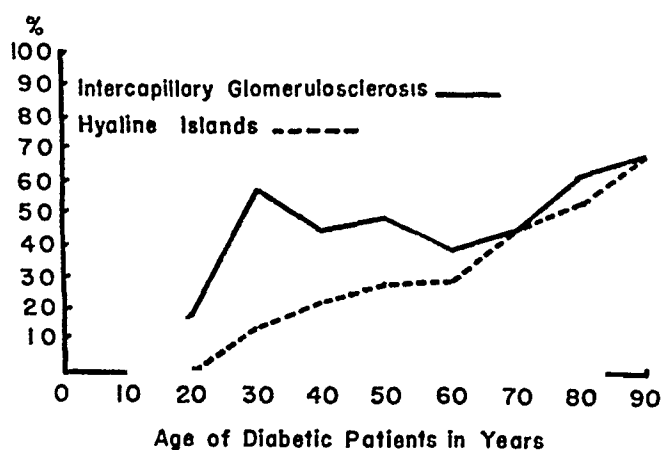


FIG 5 The incidence of intercapillary glomerulosclerosis and hyalinization of the islands of Langerhans in relation to the age of the patients

of 50 patients between five and 20 years of age without diabetes. However, in a similar number of patients without diabetes over the age of 70, the lesion was encountered in 15 cases (30 per cent). In evaluating the significance of this finding, one must consider conditions related to diabetes mellitus as being possibly associated with the glomerular change, since this lesion is so commonly found in diabetic patients. It is known that in the process of aging the glucose tolerance curve becomes altered from the normal to one approaching or resembling the diabetic type of curve. Unfortunately, these examinations were not available in the material used for this study. It is of interest to note that in the series of 50 non-diabetic patients over 70 years of age, hyalinization of the islands of Langerhans occurred in four instances (8 per cent).

*Relation to Sex* Our series of diabetic patients is composed of 107 men and an equal number of women. Intercapillary glomerulosclerosis was present in the kidneys of 38 men (35 per cent) and 56 women (52 per cent),

a ratio of 7 10 Other workers have reported a predominance in women over men, varying from 30 to 60 per cent

*Relation to Duration of Diabetes* Correlation of the incidence of intercapillary glomerulosclerosis with the known duration of diabetes mellitus reveals a constant increase in incidence with increase in duration above six years (figure 6) With known duration up to six years, the incidence of the lesion is between 30 and 40 per cent After six years it rises steadily Although the total number of patients who had diabetes mellitus for more than six years is small, a uniformly high proportion of these patients had intercapillary glomerulosclerosis This finding permits the conclusion that the diabetes precedes the renal lesion

*Relation to Treatment with Insulin* Treatment of diabetes mellitus with insulin has been suggested as a factor in the production of the glomerular lesion In 83 patients with intercapillary glomerulosclerosis in whom the

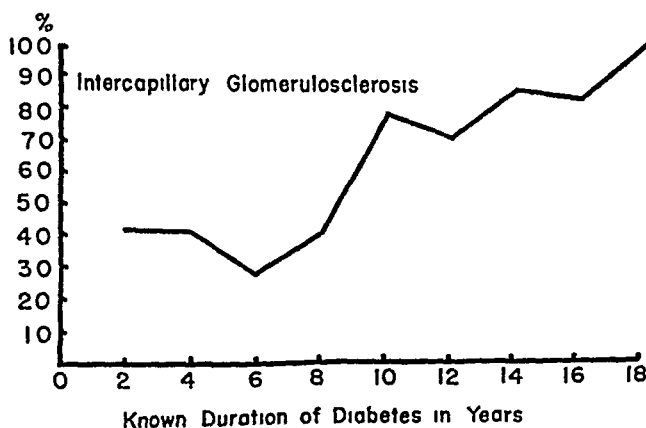


FIG 6 The incidence of intercapillary glomerulosclerosis in relation to the duration of diabetes mellitus

type of treatment is known, 50 received no treatment, 10 received insulin for less than one year, and 23 received insulin for periods varying from one to 13 years In the entire group of 214 diabetic patients, 57 received insulin for some time longer than the terminal hospital admission Of these 57 patients, 23 had intercapillary glomerulosclerosis The absence of a history of treatment with insulin in 54 per cent of the patients with intercapillary glomerulosclerosis is sufficient evidence against a relationship between treatment and the renal lesion

*Relation to Hypertension* Of our series of 214 diabetic patients, the blood pressure readings of 187 are known Of these, 81 (43 per cent) had hypertension Of 88 patients with intercapillary glomerulosclerosis in whom blood pressure readings are recorded, 44 (50 per cent) had hypertension An attempt to correlate the incidence of intercapillary glomerulosclerosis with hypertension, using enlargement of the heart as an index of the presence of hypertension, was not successful Sixty-six per cent of the

patients with intercapillary glomerulosclerosis had arteriolar changes in the kidneys, and the additional glomerular lesion is then not necessary to explain the enlarged heart. Of the 20 patients with advanced intercapillary glomerulosclerosis, 18 had arteriolar nephrosclerosis. Of 83 patients with intercapillary glomerulosclerosis in whom the weight of the heart was known, 44 (53 per cent) of the hearts weighed more than 400 grams. Of 104 patients without intercapillary glomerulosclerosis in whom the weight of the heart was known, 45 (43 per cent) weighed more than 400 grams. Of 214 non-diabetic patients, half of whom had clinical hypertension, 21 (10 per cent) had the changes of intercapillary glomerulosclerosis. In all of these cases, however, the lesions were of minimal severity. Twelve of these 21 patients had hypertension.

*Incidence in Arteriolar Nephrosclerosis* In a group of 100 non-diabetic patients with arteriolar nephrosclerosis, 11 (11 per cent) showed the presence of intercapillary glomerulosclerosis. Again the lesions were of minimal degree.

#### CLINICAL CORRELATION

Considering albuminuria as an index, one finds a distinct difference in the amount of albumin excreted by a patient with mild intercapillary glomerulosclerosis and one with advanced lesions (figure 7). In patients

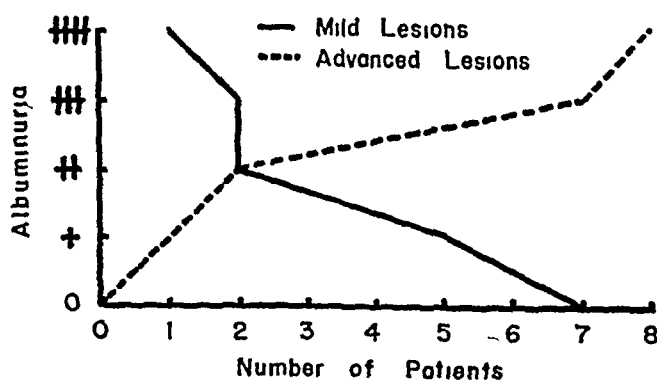


FIG 7 The correlation between the severity of the glomerular lesion and the amount of albuminuria

with mild lesions there is in general little or no albumin in the urine. Of 18 patients with advanced lesions 15 excreted large amounts of albumin. No other renal disease was found in these instances to explain the marked albuminuria. Thirty per cent of the patients with advanced lesions had advanced edema on a hypoproteinemic basis during their terminal course.

The lesion may appear at any age beyond the second decade. It is most common between 40 and 60 years of age. It is more likely to be found in women than in men, in a ratio of 10:7. The diabetes mellitus is usually mild in character and of long duration. The incidence of the glomerular

lesion rises rapidly in the group of patients who have had diabetes for more than six years

Other authors have stated that intercapillary glomerulosclerosis rarely occurs in patients without diabetes mellitus. Horn and Smetana<sup>6</sup> are the only investigators thus far who have found this lesion in a fairly high proportion of non-diabetic patients. In 214 non-diabetic patients, selected so that they corresponded in age with the diabetic patients, intercapillary glomerulosclerosis was found in 21 instances (10 per cent). In all of these cases the lesions were extremely mild. Similarly, in 100 non-diabetic patients with arteriolar nephrosclerosis, 11 instances of intercapillary glomerulosclerosis were found. In this group also the lesions were of minimal degree. It is thus evident that in the population as a whole, and in individuals with vascular disease of the kidneys, intercapillary glomerulosclerosis is present to a slight degree in one person in 10. The lesion produces no signs or symptoms, and examination of the urine and of the renal function reveals no detectable abnormalities.

When the renal lesion becomes of advanced degree it may produce the albuminuria and reduction of renal function which have been observed by other authors. As has been noted by Horn and Smetana, and confirmed by the studies reported here, these advanced lesions are present only in patients with diabetes mellitus.

Clinically, the diagnosis of intercapillary glomerulosclerosis is justified in a patient who has had mild or moderately severe diabetes mellitus for a considerable period of time, usually over six years, who begins to excrete moderate to large amounts of albumin in the urine without evidence of other renal disease to account for the albuminuria. The patient, in most instances, should be over 45 years of age and of the female sex.

#### SUMMARY

Intercapillary glomerulosclerosis occurs in 44 per cent of diabetic patients. Women are more likely to show the lesion than men, in a ratio of 10:7. It is more prevalent in patients whose diabetes is of longer duration, and who are in older age groups. There is no association with treatment with insulin. Thirty per cent of non-diabetic individuals over 70 years of age have mild lesions of intercapillary glomerulosclerosis. None are present in a group of non-diabetic patients between 5 and 20 years of age. Mild lesions are present in 10 per cent of the population as a whole. Advanced lesions are present only in patients with diabetes mellitus.

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# THE TREATMENT OF ARTHRITIC PAIN WITH DEMEROL, A NEW SYNTHETIC ANALGESIC<sup>\*</sup>

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WITH the exception of salicylates for the polyarthritis of rheumatic fever and colchicine for gout, which are more or less specific for these conditions, the treatment of the chronic pain of arthritis has always been a difficult problem. It is admitted that the commonly used analgesics, such as salicylates and amidopyrine, have some value in the mild form of arthralgias or decrease to some extent the discomfort of chronic pain, but their potency is such that analgesia is never prolonged or complete. Too often the physician must resort to opiates, a practice which unfortunately is not very satisfactory. Of the many disadvantages associated with their use, tolerance and addiction are the most important in limiting their value in the treatment of chronic pain. Fortunately a new synthetic analgesic, Demerol,<sup>†</sup> has been introduced,<sup>1</sup> which approaches the potency of morphine, but possesses an addiction liability much less than any opiate derivative<sup>2, 3, 4</sup>. Furthermore, as far as tolerance is concerned, it has been administered for many weeks or months without necessitating increasing doses to achieve the same analgesic effect.<sup>5</sup> These advantages over morphine have been utilized in the treatment of chronic arthritic pain, the result of which study is the subject of this report.

From March 1941 to date, 183 patients requiring hospitalization for severe pain associated with an arthritic condition, and 73 ambulatory patients were treated with Demerol. At the onset of the study in the hospitalized patients before sufficient experience as to the effectiveness of the drug was available, it was customary to administer a small dose of 50 to 75 mg. either orally or parenterally. If this dose proved insufficient it was increased to 100 mg. and rarely to 150 mg. In several instances, therefore, this allowed an opportunity to study the effectiveness of different doses and methods of administration. Thus, 89 patients received 92 trials of the drug parenterally, and 122 patients were treated orally for 132 trials (table 1). Both methods were used at different times in 28 patients.

Regardless of diagnosis, severity of pain, or dose, Demerol administered parenterally resulted in satisfactory analgesia in approximately 83 per cent of the trials and an additional 13 per cent had moderate relief of pain (table 2). Thus, the administration of 100 mg. parenterally every

<sup>\*</sup> Received for publication March 16, 1944.

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<sup>†</sup> Demerol is 1-methyl 4-phenyl-piperidine 4-carboxylic acid ethyl ester hydrochloride. It was introduced in Europe as "eudolat," and it was subsequently known on that continent and in South America as "dolantin." The Winthrop Chemical Company, Inc., graciously supplied us with the drug and with other aid in connection with this investigation.

TABLE I  
Scope of Investigation

Diagnosis	No of Patients	Parenterally		Orally	
		No of Patients	No of Trials	No of Patients	No of Trials
Osteoarthritis	54				
General	15	3	3	14	15
Vertebral	13	7	7	8	8
Knee	6	4	4	2	2
Shoulder	7	2	3	5	5
Hip	4			4	5
Sacroiliac	9	5	5	5	6
Sciatic syndrome	40	24	26	22	24
Rheumatoid arthritis	23	12	12	17	18
Infectious arthritis	16	7	7	11	13
(Non-specific etiology)					
Gout	5	2	2	3	3
Spondylitis (Marie-Strumpell)	1			1	1
Gonococcal arthritis	11	6	6	8	9
Polyarthritis (rheumatic fever)	18	5	5	17	18
Bursitis	12				
Subdeltoid	7	6	6	2	2
Olecranon	2	1	1	1	1
Gluteal	2	2	2		
Patella	1			1	1
Myositis	3	3	3	1	1
Total	183	89	92	122	132

four hours was sufficient in the majority of patients completely to control the pain for three or more hours or to give almost complete relief of pain for several hours. This was attained with few or no untoward reactions. In spite of prolonged administration, in many instances for weeks and months, the same result was achieved as long as the medication was given at regular intervals.

Excellent results were obtained in alleviating the pain of the sciatic

TABLE II  
Effectiveness of Demerol in Terms of Dose Administered both Parenterally and Orally, Regardless of Diagnosis or Severity of Pain

Administered Parenterally										Administered Orally									
Dose Mg	No of Trials	Complete		Moderate		Slight		None		No of Trials	Complete		Moderate		Slight		None		
		No	%	No	%	No	%	No	%		No	%	No	%	No	%	No	%	
50	2	1	—	1	—	—	—	—	—	32	22	68.7	4	12.5	4	12.5	2	6.3	
75	9	4	44.4	3	33.3	—	—	2	22.2	8	5	62.5	2	25.0	1	12.5	—	—	
100	80	70	87.5	8	10.0	2	2.5	—	—	92	55	59.8	18	19.5	9	9.8	10	10.9	
150	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Total	92	76	82.6	12	13.0	2	2.2	2	2.2	132	82	62.1	24	18.1	14	10.6	12	9.1	



syndrome regardless of causation. Similar effects were noted in patients with myositis, acute bursitis, advanced osteoarthritis, rheumatoid, gonococcal, and non-specific infectious arthritis. Particularly striking was the relief of secondary muscle spasm and increased mobility of the joint following prolonged administration of Demerol.

When Demerol was administered orally, completely satisfactory results were achieved in 62 per cent of the 132 trials and in an additional 18 per cent of the trials there was moderate relief of pain. From table 2 it would appear that approximately the same relief is obtained with 50, 75, or 100 mg. Actually, when one considers the results in terms of diagnosis it is evident that a greater response is obtained with the higher doses. As in the case of the parenteral route good results are obtained with oral Demerol in the sciatic syndrome, osteoarthritis, infectious non-specific arthritis, gonococcal and rheumatoid arthritis. Only in the case of polyarthritis due to rheumatic fever are the results unsatisfactory. With this condition only 50 per cent (nine out of 18 trials) had relief of pain with the drug administered orally.

The treatment of the ambulatory patient is complicated by the fact that a high percentage of such patients experience unpleasant side reactions. Since these may take the form of dizziness, nausea, vomiting, and rarely syncope, it is very difficult in certain individuals to obtain a satisfactory response. Thus, in the group of 73 ambulatory patients, unsatisfactory relief of pain was noted in 29 (table 3). Twenty-two of these had moderate to severe side reactions overshadowing any analgesic effect of the drug and

TABLE III  
Effectiveness of Demerol Administered Orally to Ambulatory Patients

Diagnosis	No of Patients	Effectiveness			
		Complete	Moderate	Slight	None
Osteoarthritis	21	7	1	5	8
General	6	2	2	1	1
Vertebral	4	3	—	1	—
Knee	7	6	—	—	1
Shoulder	2	2	—	—	—
Hip	2	—	—	—	2
Sacroiliac					
Total	42	20	3	7	12
Rheumatoid arthritis	14	7	1	3	3
Spondylitis (Marie-Strumpell)	1	1	—	—	—
Infectious (non-specific) arthritis	5	3	—	—	2
Gout	3	2	1	—	—
Bursitis—subdeltoid	5	3	—	1	1
Bursitis—gluteal	1	1	—	—	—
Myositis	2	2	—	—	—
Total	73	39	5	11	18
Per cent		53.4	6.8	15.0	24.7

also acting as a barrier for continuation of the medication and proper adjustment of the dose. Although the results indicate that only 53 per cent of the cases had relief of their arthritic pain, the incidence of satisfactory response would have been higher if those patients having an untoward reaction would have continued taking the medication. This is because tolerance to the side reactions develops very quickly, thus allowing the analgesic effects to become manifest. Many patients gradually obtained greater and more prolonged relief of their pain even though they may have experienced some reactions at the onset of therapy. For this reason it is advisable when initiating the use of Demerol for ambulatory patients to start with a small dose, usually 25 mg, for the first few days until the tendency to untoward reactions subsides. No attempt should be made to achieve analgesia during this phase of therapy, but as soon as possible the dose should be increased to 50 or 100 mg every four hours. This regime invariably gives satisfactory results regardless of the type of arthritis or severity of the pain.

Although for the purpose of this study, orthopedic and other corrective measures were limited wherever possible, it must be remembered that Demerol can only give symptomatic relief of pain and that these measures should be instituted if indicated.

In conclusion, although insufficient cases are available for a statistical survey of the effectiveness of Demerol in any specific arthritic condition, it is apparent that the drug is of definite value in the treatment of chronic pain associated with arthritis. Hospitalized patients respond to a degree comparable to the effects expected with morphine. However, the dangers of addiction are minimal and the incidence of side reactions is much lower. Ambulatory patients can also be treated satisfactorily if the dose is determined individually for each patient and time is allowed for untoward reactions, if any, to subside.

I am indebted to Miss Aniele C. Evaskitis and Miss Gwendolyn M. Newhook, research nurses of the Department of Therapeutics, New York University College of Medicine, for their invaluable assistance in obtaining data on patients receiving Demerol.

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# SEVERE ASTHMATIC DYSPNEA AS THE SOLE PRESENTING SYMPTOM OF GENERALIZED ENDOLYMPHATIC CARCINOMATOSIS

## REPORT OF TWO CASES WITH AUTOPSY FINDINGS AND REVIEW OF THE PERTINENT LITERATURE\*

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It is common knowledge today that respiratory symptoms are not infrequent manifestations of malignant disease arising elsewhere than in the lungs. Metastases to the lung are of fairly common occurrence in a great variety of carcinomata, these metastases usually occur as nodular, solid, or linear masses, without constant relationship to lymphatics, arterioles, or venules. Less commonly, the neoplastic cells are found almost exclusively within the pulmonary lymphatics, and may in addition permeate the venules or arterioles. This type of "carcinomatous lymphangitis" was first described by Andral,<sup>1</sup> mentioned again by Vichow,<sup>2</sup> and more fully elaborated by Troiser.<sup>3</sup> The frequency with which this histological picture is found has been appreciated much more fully in Europe than in America, and it is only within recent years that the peculiar aspects of the clinical picture to which it can give rise have been studied. Unfortunately, most of the reported series of cases presenting the pathological picture outlined above have not carefully distinguished between those cases in which other clinical evidences of malignancy were present and those in which pulmonary manifestations were the sole or predominant features of clinical syndromes difficult of diagnosis and resistant to any therapy.

It is the purpose of this paper to report two cases in which pulmonary metastases from intra-abdominal cancer gave rise to a clinical syndrome so typical that therapeutic regimes routine for that syndrome were instituted, without suspicion of the underlying malignant process. In both these cases the syndrome was asthmatic dyspnea and the underlying pathological process pulmonary endolymphatic carcinomatosis. In neither instance were there any signs or symptoms referable to the primary site of the tumor, nor did clinical and roentgenological investigations disclose any evidence of metastases to other organs. A brief review of the clinical, pathological, and physiological features of pulmonary endolymphatic carcinomatosis follows the case reports.

### CASE REPORTS

*Case 1* This 28-year-old, American-born, single factory worker was admitted to the hospital in December with the chief complaint of acute respiratory distress.

\* Received for publication May 15, 1944.

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.

For four months she had had progressive shortness of breath following a rhinitis and conjunctivitis in August. During the entire year before entry she had been somewhat apathetic and listless and had lost a little weight. Two months before hospitalization she had begun to wheeze and became subject to paroxysms of violent coughing, at the end of which bouts she often vomited up clear gastric fluid. No other gastrointestinal disturbances were noted. Two weeks prior to entry she had a mild shaking chill with some pain in the left lower chest and epigastric soreness after coughing. For the week preceding admission she had had frequent chilly sensations, associated with definitely wheezy breathing, on the morning of admission she had an acute attack of wheezing dyspnea. Past history revealed that the patient had suffered from hay fever and possibly from mild asthma for the past two ragweed seasons. She had worked in textile finishing plants for several years, where she was exposed to wool dusts, but she had not been subjected to this exposure for the three months preceding admission. There was no history of eczema, angioneurotic edema, or urticaria. There had been a "nervous breakdown" nine years prior to entry, and there was a well-documented history of nightmares, temper tantrums, and nervous instability. Otherwise, she had been in good health. Family history and social history were not in any way remarkable.

Physical examination disclosed a well-developed, well-nourished, acutely ill young woman with temperature 101.2° F by rectum, pulse 160, respirations 28 per minute. She was cyanotic, orthopneic, perspiring, and coughing paroxysmally. Occasionally she vomited clear gastric contents after a severe bout of coughing. There was audible wheezing. Throat and tonsillar fossae were reddened, the neck was supple, the thorax was symmetrical with slightly increased anteroposterior diameter and moved, as a whole, with all the accessory muscles of respiration in use. There were no signs of consolidation, expiration was prolonged, and the chest was full of squeaks and wheezes. The heart, abdomen, genitalia, rectum, and nervous system were not remarkable. Blood pressure was 118 mm Hg systolic and 90 mm diastolic.

*Laboratory Data* The blood Hinton and Wassermann reactions were negative. Urinalysis, hematocrit, sedimentation rate, hemoglobin, blood urea nitrogen, serum protein, and fasting blood sugar determinations were within normal limits. The leukocyte count was 15,000 per cubic millimeter on admission, with a normal differential count. Gastric contents and stools were guaiac-negative on two occasions. The vital capacity was 400 cubic centimeters. A roentgen-ray film on admission showed extensive, rather marked involvement of both lungs with peculiar diffuse streaking suggesting pulmonary fibrosis alternating with small circular clear areas of lobular emphysema. The hilar shadows were enlarged and "inflammatory" in appearance. An electrocardiogram showed a sinus tachycardia, with low EMF and abnormal QRS.

*Hospital Course* The patient was given oxygen, which reduced her pulse rate from 160 to 120 per minute, at which rate it remained for the greater part of her hospital stay. The wheezing, however, was not relieved by oxygen, by epinephrine, or by the usual antispasmodics, including 0.48 gram of aminophylline intravenously. Estimation of the oxygen saturation of her capillary blood showed that when she breathed room air her saturation was 81 per cent (normal 95-98 per cent), after she had inhaled 80 per cent oxygen for one hour, the saturation had risen to 100 per cent. Another roentgen examination showed much the same picture as before, with increased reaction around the hilar nodes. The liver became palpable one finger's breadth below the costal margin and was slightly tender. She died on the nineteenth hospital day.

*Clinical Impression* The majority opinion was that the patient's respiratory difficulties resulted from a generalized pulmonary fibrosis, probably caused by a chronic pneumonitis of virus etiology.

*Autopsy* A generalized carcinomatosis was the striking finding. The left lobe of the liver was so completely replaced by tumor that its edge was smooth and not nodular. There was extensive involvement of the abdominal lymph nodes, the peritoneum, and the ovaries. The lungs presented an interesting appearance. They remained distended after the thorax was opened, and the pleurae showed extensive patches of thickening, in most areas following the distribution of the pleural lymphatics. The cut surfaces showed an unusual, mosaic-like pattern in which small areas of atelectasis appeared to alternate with areas of emphysema. The stomach was not remarkable except for a tiny hard nodule in the pyloric mucosa, 4 mm in diameter, which was fixed, but not ulcerating.

Microscopic examination showed the small nodule in the pylorus to be made up of neoplastic epithelial glands and abundant stroma, with many adjacent large lymphatics distended with tumor cells. The lung tissue showed extensive infiltration with the same kind of cells. The largest masses of these cells were found in the distended peribronchial and perivascular lymphatics. In the instances where the tumor was found infiltrating the walls of the bronchi and larger blood vessels as well as the pleura, delicate, actively proliferating connective tissue stroma could be seen. Clumps of tumor cells were identified within blood vessels of larger caliber. Nodules in the liver and the abdominal lymph nodes and viscera showed much the same picture of infiltration by tumor cells originating in the pyloric area.

*Summary of Case* A 28-year-old single woman entered the hospital in an acute asthmatic state, following four months of progressive wheezing dyspnea. She had felt tired for a year, but had no specific complaints until her respiratory difficulties began. To physical examination she revealed only cyanosis and markedly wheezy dyspnea. Laboratory data were not remarkable. The roentgen films showed generalized reticular shadows in the lung, with enlarged hilar nodes. She did not respond to any of the usual bronchodilators, and died on the nineteenth hospital day. Autopsy revealed widespread endolymphatic metastases from a small adenocarcinoma of the pyloric region. There was extensive carcinomatous permeation of the peribronchiolar lymphatics with some infiltration of pulmonary blood vessels (figure 1).

*Case 2* The patient was a 38-year-old single, white, American-born sales girl who entered the hospital with an eight weeks' story of pleuritic pain, cough, and wheezing. She had been in excellent health until nine weeks before entry, at which time she had a low-grade lumbar backache, seven days later this complaint bothered her enough to force her to take to bed. Two days later she had a sudden chill, lasting 5 to 10 minutes, and developed a hacking cough. She complained of pain in her lower left chest, and was treated by her physician by means of mustard plasters and cough remedies, with some relief. From the onset of her cough she had been short of breath, and for the four weeks prior to entry she had been wheezing severely. There had been some sudden sweats, occasionally as often as four times a day, but the outstanding complaints had been dyspnea, orthopnea, and wheezing, associated with paroxysms of nonproductive coughing. She had become anorexic and had lost 12 pounds. There were no symptoms referable to other systems. There was no history of previous asthma, hay fever, or other allergic manifestations. Past history revealed that the patient had always enjoyed good health, she had been subject to occasional head colds and believed that she had enlarged adenoids. She had missed her last menstrual period. Family history and social history were not remarkable.

Physical examination disclosed a well-developed and well-nourished woman of the stated age who was propped up in bed and appeared acutely ill. She was mentally alert, but slightly cyanotic and gasping for breath. The respiratory rate was 32 per minute, the temperature 100.6° F by rectum. The skin was pale, without eruptions, pigmentation, or jaundice, and was cold and clammy over the extremities. The lips and finger nails were cyanotic. Eyes, ears, nose, and throat were not signifi-



Fig 1 Case 1 Section of small bronchus Carcinoma is seen permeating lymphatics, venules, and arterioles There is a marked inflammatory reaction

cantly abnormal. The thorax was symmetrical, moved as a whole, and expiration was prolonged and labored. The lungs showed impaired resonance to percussion at both bases with some signs of consolidation at the left base. There were loud expiratory wheezes over the entire chest. The heart seemed slightly enlarged, but was otherwise normal except for a tachycardia of 120. The blood pressure was 138 mm Hg systolic and 86 mm diastolic. The abdomen contained no palpable viscera, was not distended, and showed no signs of fluid. Pelvic and rectal examination revealed no abnormalities. Neurological examination was not remarkable.

*Laboratory Data* The blood Hinton and Wassermann reactions were negative, the urine was not remarkable. The blood showed a hemoglobin of 85 per cent (Sahli), an erythrocyte count of 40 million per cubic millimeter, a leukocyte count of 10,900 per cubic millimeter, with normal differential. One stool showed a positive guaiac reaction. A bedside roentgen film disclosed a diffuse fine mottling throughout both lungs. Intracutaneous test with old tuberculin 1:10,000 was positive.

*Hospital Course* From the outset the patient's main difficulty was respiratory, her dyspnea, wheezing, and tachycardia were treated with sedation and oxygen, without relief. A strenuous antiasthmatic regime utilizing the usual antispasmodics produced some amelioration of the wheezing without altering in the least her progressively downward course. Her pulse rose to 140-150 per minute, her respirations to 40 per minute, and she died on the fourth hospital day.

*Clinical Impression* There was no unanimity concerning the diagnosis, but diffuse acute pneumonitis and miliary tuberculosis were thought to be the most probable causes of the acute asthmatic dyspnea.

*Autopsy* A generalized carcinomatosis was evident on opening the abdomen. The retroperitoneal area was filled with a mass of indurated para-aortic lymph nodes, most marked at the level of the left kidney, but extending all along the aorta from its bifurcation up to and through the diaphragm. No primary tumor could be palpated. The right cavity contained 100 cubic centimeters of blood-tinged fluid. The left pleural space was clear. There were extensive fibrinous adhesions over both left lung lobes. After the thorax was opened, the lungs remained firm and on cut section showed a "sandpaper appearance," with lymphatics and venules outlined as hard, firm cords. The pleural surfaces also showed cords of firm tissue, and the tracheobronchial lymph nodes were invaded and partially replaced by tumor tissue. The pancreas was completely surrounded by massive cancerous nodes.

On microscopic examination the lungs showed greatly dilated lymphatics and partially recanalized thrombi in the veins, both lymphatics and veins contained masses of tumor cells. The tumor tissue was for the most part undifferentiated, but manifested a slight tendency toward an acinar arrangement. The alveoli were invaded here and there, but the tumor cells lay largely within the veins and lymphatics. Other abdominal viscera were similarly involved. The lumbar vertebrae and rib marrow were filled with these neoplastic cells, and there was hematopoiesis in the liver and spleen.

The pathologist interpreted this picture as that of adenocarcinomatosis, probably arising from aberrant pancreatic tissue in the retroperitoneal spaces.

*Summary of Case* A 38-year-old single woman gave an eight weeks' story of pleuritic pain, cough, and wheezing, with sudden onset marked by chills. In excellent health beforehand, she gave no symptoms referable to disturbances of other organ systems. Physical examination was remarkable only for cyanosis and the signs of asthmatic dyspnea, with minimal consolidation at the left lung base. Laboratory data were noncontributory except for one guaiac-positive stool. The roentgen film showed a fine mottling throughout both lungs. She died on the fourth hospital day while under intensive therapy with oxygen and antispasmodics. Autopsy

showed a generalized endolymphatic carcinomatosis, probably originating in aberrant pancreatic tissue. Pulmonary lymphatics and smaller blood vessels were extensively invaded by the tumor cells.

### DISCUSSION

These two patients belong to that relatively small group of cancerous subjects presenting diagnostic problems in dyspnea, in whom the respiratory embarrassment is so severe that general symptoms, which under other circumstances might be attributed to malignancy, are discounted as being secondary to the respiratory difficulties. The two cases here reported are unusual in the literature because they presented only dyspnea of the asthmatic type, otherwise, they are in no way distinct from other cases showing dyspnea due to "carcinomatous lymphangitis"<sup>1</sup> of the lung, and the following remarks will stress those features they share in common with the whole group rather than those features in which they differ.

### CLINICAL PICTURE

As a general rule, respiratory symptoms in these cases depend primarily upon whether the tumor cells have obstructed the smaller pulmonary arterioles to a degree sufficient to cause pulmonary hypertension, or whether the infiltration is predominantly endolymphatic and peribronchiolar. In the former type, described first by Schmidt,<sup>4</sup> and well reviewed recently by Greenspan,<sup>5</sup> symptoms and signs of right-sided heart failure may be the presenting features. In the latter type, into which category the present cases fall, symptoms are more strictly referable to interference with respiratory exchange and with the normal activity of bronchial musculature.

*1 Age and Sex Incidence.* In an analysis of 49 cases from the literature, Wu<sup>6</sup> found that 8 per cent occurred in the second decade of life, 28.6 per cent in the third, 28.6 per cent in the fourth, 20.4 per cent in the fifth, 6.1 per cent in the sixth, and 4.0 per cent in the seventh decade. This collection of pathological data includes several cases of bronchogenic cancer, however, which do not properly belong in a group of cases presenting primarily metastatic phenomena such as that we are now considering. He added five cases of his own, which followed the same age distribution as does the larger series, but again he included one case of primary carcinoma of the bronchus in this group. In addition, none of his cases presented primarily respiratory difficulties, and all of them had other evidences of malignant disease. In a similarly comprehensive and nonselective review, Poppi<sup>7</sup> found that the average age at onset of all cases was 42.6 years, but that in those cases with metastases from carcinoma of the stomach the average was 38 years.

Wu's figures show 65.3 per cent of the cases occurring in males, 34.7 per cent in females, Poppi gives the incidence as 53 per cent in males, 47 per cent in females. The discrepancy arises primarily because of the small number of cases in each series.



## 2 *Symptoms and Signs*

(a) Dyspnea, severe, unremitting, and progressive, is the most common and distressing complaint of these patients. It is characterized<sup>7</sup> by a gasping tachypnea, usually of 26–45 respirations per minute, and is present when the patient is at rest in bed. The onset is usually insidious, but it may be precipitated by, or occur simultaneously with, an upper respiratory infection. In an interesting case reported by Gaines<sup>8</sup> the initial symptoms were cough and dyspnea following the inhalation of large quantities of dust, steadily progressing dyspnea was found to result from extensive pulmonary endolymphatic carcinoma metastatic from the stomach. Physical signs in the chest have been usually much less striking than the degree of dyspnea would seem to warrant, scattered fine râles, a small hydrothorax, and poor excursion of the diaphragm are the usual findings. In the cases reported here, of course, the striking feature was asthmatic wheezing. Signs of right-sided heart failure may be found in those patients in whom the neoplastic infiltration has invaded the arterioles of the pulmonary circulation.

(b) Cough occurs in about 50 per cent of the reported cases, it is dry, hacking, frequently paroxysmal, and usually productive of nothing more than a little blood-stained froth or dry, sticky mucus. It is very difficult to control by therapy.

(c) Chest pain of some degree is found in 10 per cent of the reported cases. It is characteristically pleuritic in nature, and may often be due to involvement of ribs or vertebrae with carcinoma. When one considers the extensive infiltration of the pleurae encountered histologically in nearly all these cases, it is surprising that true pleuritic pain does not occur more frequently.

(d) Cyanosis is a variable feature of the disease. Case 1 here described presented an arterial oxygen saturation of only 81 per cent, which was quickly restored to normal upon the administration of oxygen. The tachypnea is not affected by oxygen therapy, however. In several reported cases<sup>5</sup> "Ayerza's syndrome" (Montgomery<sup>9</sup>) has been produced by extensive thrombo-endarteritic carcinomatosis, with resulting pulmonary hypertension. This hypertension must be of a significant degree, for most of these patients were young, and possessed presumably good myocardial reserve.

(e) A fever of 99.6 to 101° F is exhibited by most of these patients when they are admitted to hospitals. The temperature curve is not diagnostic or in any way remarkable.

(f) Weight loss, anorexia, and other nonspecific manifestations occur often in the reported series, and the total duration of the illness shows a wide variation from case to case. It should be emphasized again that most of the cases reported in the literature as showing by autopsy pulmonary endolymphatic carcinomatosis did not present primarily diagnostic problems in dyspnea. The latter was often the factor that precipitated hospitalization,

but it usually followed two to 15 months of progressive weakness, anorexia, and other symptoms due to advanced malignant disease. In the group with which we are primarily concerned here, dyspnea has its onset within four or five months, usually within two months, of the time of hospitalization. The distress produced by the tachypnea and cough over a period of several months usually causes inanition adequate to explain moderate weight loss and weakness. On the other hand, marked emaciation, vomiting, and grossly bloody stools are presumptive evidence of disease elsewhere than in the respiratory tract, and patients presenting these advanced manifestations are not ordinarily considered as diagnostic problems in the causation of dyspnea.

3 *Laboratory Data* It may be categorically stated that the examination of blood and urine offers little or no information of diagnostic significance in these cases. There may be a compensatory erythrocytosis, and those patients in whom terminal bronchopneumonia develops may present the features of that disease. Examination of pleural fluid, if any effusion is present, may demonstrate the presence of tumor cells.

4 *Roentgenological Picture* The first detailed description of endolymphatic carcinomatosis as seen on the roentgen film was made by Assman,<sup>10</sup> who characterized the picture as a pattern of thin lines extending from the hilum towards the periphery, with frequent reticulation. The hilar nodes are usually enlarged. Unless actual nodules are present, the picture is more often suggestive than diagnostic, similar findings may be observed in pneumoconioses, miliary tuberculosis, lymphoma, and postinfectious fibrosis. In a very recent case<sup>11</sup> the roentgen film was suggestive of multiple bronchiectatic abscesses. Signs of right-sided cardiac enlargement may be observed in those cases with a significant amount of thrombo-endarteritis of the pulmonary circulation. Schwarzmunn has recently reviewed<sup>12</sup> these features and has added two new cases.

#### PATHOLOGICAL FINDINGS

The usual picture at autopsy has been well summarized by Schattenberg and Ryan as follows: "The lung is larger, firmer, and more moist than normal. There is a dilatation of pleural lymphatic channels which causes them to stand out prominently, and the lobules of the lung are characteristically delineated. At the point of intersection of the lymphatic channels small yellowish-white nodules may be seen. On cut section the lung appears mottled and similar involvement of peribronchial and perivascular lymphatics is seen. Small plugs can be expressed sometimes from these involved vessels. Microscopically, tumor cells are found filling the perivascular, peribronchial, and pleural lymphatics. In many cases, tumor cells are also found in the vessels of the alveolar walls, and there is often noted an intimal proliferation, sometimes elliptical in nature, which more or less occludes the arterioles."<sup>13</sup>

Wu<sup>6</sup> analyzed his collected series for primary foci and found that 73.5 per cent of his 49 cases had tumors originating in the stomach, 10.2 per cent in the bronchus, 6.2 per cent in the breast, 4.1 per cent in the prostate, 2.0 per cent in the uterus, 2.0 per cent in the sigmoid, and 2.0 per cent in the gall-bladder. A review of 4,892 autopsy protocols at the Peter Bent Brigham Hospital discloses that only 96 cases are classified as showing significant pulmonary metastases from tumors originating elsewhere than in the lung. Of this group, 30 cases showed metastases which were predominantly endolymphatic in type. These 30 metastatic tumors originated from tumors primary in the following organs: stomach (seven cases), breast (seven cases), prostate (four cases), pancreas (three cases), testis (two cases), liver (two cases), pharynx, bladder, appendix, gall-bladder, and rectum (one case each). Of the entire group of 30 patients, nine had prominent respiratory symptoms, but only the two cases reported in detail here had no other clinical evidence of malignancy.

The pathogenesis of the metastatic processes has been ably discussed by Greenspan<sup>5</sup>. He concludes that metastases to the lung may occur by direct extension along venous or lymphatic pathways, and that direct compression of bronchioles and blood vessels results from invasion of these structures by cells lodged in the surrounding lymph and venous channels. This theory was originally suggested by Girode,<sup>14</sup> and is opposed to that of Schmidt,<sup>41</sup> who supposed that tumor emboli were trapped in the small terminal arterioles and venules. That the lymphatic networks of the lungs should be completely filled by neoplastic cells derived from tumors originating in the abdominal cavity is not surprising when one considers the rich interlacing plexus of lymph channels which drains the thoracic and peritoneal cavities. Rouviere comments as follows: "The subperitoneal and subpleural networks of the diaphragm are not independent of one another. Quite the contrary. They are intimately united by numerous lymphatic vessels. These direct lymphatic communications between the networks of the peritoneal and the subpleural surfaces of the diaphragm explain the possible transmission of subdiaphragmatic peritoneal inflammation to the pleura and vice versa."<sup>15a</sup> Rouviere's observations show that the lymphatics of the lungs also communicate with abdominal lymph channels through connections with the lateroesophageal and juxtaortic lymphatic network.<sup>15b</sup> Drinker and Yoffey state: "If lymph flow is obstructed, as occurs in silicosis, lymph will back up into the vessels along the vein, and will be forced over into the subpleural group of lymphatics."<sup>16</sup> These metastases apparently occur more often in younger than in older patients. McNeer,<sup>17</sup> in a recent study of the occurrence of gastric cancer in a group of 501 persons under 31 years of age, noted that the incidence of significant pulmonary metastases was 10.2 per cent, a figure considerably greater than that found in analyses of gastric carcinoma in all age groups.

## PHYSIOLOGICAL CONSIDERATIONS

The mechanism of dyspnea in these unfortunate patients is presumably the resultant of several factors. The actual permeation of the perivascular and peribronchiolar lymphatics by solid cords of tumor cells may mechanically obstruct normal gas diffusion across the respiratory epithelium. Secondly, and probably more importantly, there is almost always an inflammatory response around these invading cells, producing at first interstitial edema and hyperemia, and, after a period of time, a stiffening and inflexibility of both conducting and respiratory portions of the respiratory tree. Thirdly, these same cells, lying adjacent to and frequently invading the bronchial musculature, may actually impair the structural and functional integrity of that musculature. The effect of all three factors is probably to keep up a constant stimulation of afferent stretch nerve fibers, the sensory endings of which are located in bronchial and bronchiolar walls. The resulting impulses are carried into the spinal cord either directly by the dorsal sympathetic nerves, or pass through the stellate ganglion<sup>18, 19</sup>. After ascending in the cord to the region of the fasciculus solitarius, they arouse efferent impulses of bronchoconstriction, which are mediated through the vagus<sup>18, 20</sup>. The distended alveoli, edematous and rigid bronchi, and poor gas exchange result in a cycle characterized by the constant reflex inhibition of an inspiratory center already depressed by anoxia. The hyperpnea and tachypnea consequent upon this inspiratory inhibition further deplete the blood of carbon dioxide, and central chemical regulation of respiration becomes inefficient. In the chronic asthmatic, who presents a similar picture, Miscall and Rovenstine<sup>18</sup> have shown that interruption of afferent bronchoconstrictor fibers at the stellate ganglion and at T2, T3, T4, gives a considerable degree of relief from the severe gasping dyspnea which so disturbs this type of patient. In addition to these important reflex factors, the effect of the impairment of bronchial contractility and extensibility in itself may be inferred from the success Barach<sup>21</sup> has reported in treating asthmatics by "repeated bronchial relaxation" over periods of several days. The slight response to antispasmodic therapy manifested by the carcinomatous patients here described can probably be attributed to irreversible changes in the bronchial musculature produced by invasion and inflammatory reaction. In view of the rapidly progressing downward course these patients exhibit, heavy sedation is probably the therapy of choice.

## SUMMARY AND CONCLUSION

1 Two cases of endolymphatic carcinomatosis metastatic to the lung are reported. In one case, the primary cancer was gastric, in the other, the primary tumor presumably arose in aberrant pancreatic tissue.

2 These cases, unlike most other reported cases with the same underlying pathologic lesions, presented signs and symptoms of severe asthmatic

dyspnea, not associated with other clinical evidences of malignancy. One patient had a past history of hay fever. Both were treated as asthmatics, with negligible therapeutic effect, and both died with then basic lesions undiagnosed.

3 A review of the literature discloses that the syndrome ought to be suspected in any patient, whether young or old, who develops, either suddenly or insidiously, a rapidly progressive tachypnea, associated usually with cough, occasionally with cyanosis, and sometimes with pleuritic pain. Signs of right-sided heart failure may be found. In most cases, other evidences of malignancy may be elicited, but a small number of cases present only a severe dyspnea, with or without wheezing. The roentgen film is occasionally diagnostic, but more often only suggestive. Laboratory data are usually non-specific.

4 A brief review of the clinical, pathological, and physiological features of the disease is included.

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# "CHOKES": A RESPIRATORY MANIFESTATION OF AEROEMBOLISM IN HIGH ALTITUDE FLYING<sup>1</sup>

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THE tactical success of certain operations in this war has required aircraft capable of flying in the stratosphere. To keep pace with the accomplishments of the aeronautical engineer, the physiologist has had to study man's tolerance for and means of protecting him from three major hazards of the stratosphere: lack of oxygen, extreme cold, and low atmospheric pressure. The disease produced by exposure to rapid decrease in atmospheric pressure, such as encountered in the ascent of aircraft to high altitude, is called aeroembolism or decompression sickness. The manifestations of this disease are numerous. Armstrong<sup>1</sup> has grouped them in order of frequency according to systems: structural, dermal, cerebrospinal and respiratory. Among these he mentions joint pains, thermal hyperesthesia, pruritus, neuritis, paralysis, convulsions, pulmonary pain, pulmonary edema, cough and expectoration.

Although joint pain is by far the most frequent manifestation of aeroembolism, respiratory symptoms commonly called "chokes" are alarming and sometimes serious disorders, engendered by exposure to reduced atmospheric pressure. In this article we present the results of studies made on 132 cases of chokes occurring in 329 young men making 719 "flights" in a decompression chamber. We have analyzed some of the clinical features of chokes, and we have investigated certain factors that might influence the incidence and severity of chokes, namely: altitude, exercise at altitude, severity of the chamber test, time of day and age. Although these studies have been carried out in a low pressure chamber, it is of interest to point out that in a recent series of 25 airplane flights at 35,000 feet, we have observed in a large group of subjects and crew members that the incidence and nature of symptoms of decompression sickness are the same as those observed in the chamber at simulated altitudes. For reasons of security many important data could not be included in this article.

## METHODS

The experiments were carried out in a decompression chamber in which it was possible to simulate the pressure conditions encountered at any altitude. All subjects were young male students who had passed a military physical examination. Except in the preoxygenation studies, subjects used in one

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From the Aeromedical Research Laboratory, University of California, Berkeley.

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experiment were generally not used in another experiment. Essential data on each experiment are given in table 1.

A 30 second, 10 step-up exercise onto a nine-inch stool was used in these studies. The subjects performed this exercise immediately upon reaching altitude and at  $2\frac{1}{2}$  or 5-minute intervals thereafter until they developed symptoms severe enough to cause descent or until they had remained at altitude for the full test period (90 minutes). When not exercising, they sat as quietly as possible in their chairs. Ascent to altitude was made at the rate of 3,170 feet per minute and constant flow oxygen breathing (99.5 per

TABLE I  
Data on Experimental Procedure

Peak altitude in feet	38,000	38,000	38,000	38,000	38,000	30,000	30,000	33,750
Corresponding pressure in mm Hg	154.9	154.9	154.9	154.9	154.9	225.6	225.6	189.0
Frequency of exercise at altitude in minutes	5	5	5	5	$2\frac{1}{2}$	$2\frac{1}{2}$	5	5
Rate of ascent in feet per minute	3,170	3,170	3,170	3,170	3,170	3,170	3,170	3,170
Time of oxygen inhalation to altitude in minutes	9	21	60	120	9	9	9	9
Time of oxygen inhalation to 10,000 feet in minutes	0	12	51	111	0	3	3	$1\frac{1}{2}$
Time at altitude in minutes	90	90	90	110	90	90	90	90
Number of subjects	68	61	61	61	45	50	58	47
Number of chamber flights	136	61	61	61	90	100	116	94

*Note.* Frequency of exercise referred to above and in subsequent tables and figures, is defined as the interval between the beginning of each successive exercise.

cent oxygen) was started as shown above. While at altitude, they recorded their symptoms on individual flight symptom sheets and rated the intensity of symptoms by a nine-point scale. A physician interviewed each subject at the termination of his flight. The 61 subjects in the preoxygenation series each made three acceptable flights with 12, 51 and 111 minutes of preoxygenation. The time of preoxygenation here refers to the number of minutes the subjects spent inhaling pure oxygen prior to ascent and up to 10,000 feet during ascent. Each subject in the other experiments made two acceptable flights. For the purpose of these studies, an acceptable flight was defined as one terminated prematurely by chokes or by joint pain or one during which the subject remained the full time at altitude. Although flights in the 111 minute preoxygenation experiment lasted 110 minutes (20 minutes longer than all other experiments), no subject in the experiment



developed joint pain or chokes or descended prematurely after 90 minutes at altitude

A small amount of water was placed in the economizer bags of the oxygen masks to avoid irritation of the respiratory tract by dry oxygen

### SOME CLINICAL FEATURES OF CHOKES

In our experience, chokes are recognized by three major symptoms—chest pain, cough and dyspnea. Chest pain and cough usually appear together, although one or the other often occurs as the sole manifestation of chokes. Dyspnea appears most frequently in the more severe cases and always in combination with chest pain or cough. The pain is invariably substernal, it does not radiate to the arms, neck, jaw or abdomen. It is usually relieved during descent, though an uncomfortable chest sensation may persist for several minutes after reaching ground level. The cough is non-productive at altitude and there is no sign of hemoptysis. The act of coughing does not relieve the desire to cough. When established at altitude, the cough usually continues during descent, is often intensified during recompression, and may also last several minutes after reaching ground level. In rare cases it has endured a few hours. Though subjects with severe chokes may show pallor or flushing, cyanosis has not been observed in our cases.

To initiate the present study, we divided chokes into four categories based on severity—incipient, mild, moderate and severe. The division depended on clinical judgment and required weighing the amount of pain or cough and dyspnea. A brief description of each category has been presented in a previous report<sup>2</sup> from this laboratory. Among 132 cases of chokes in the present study, 40 were incipient, 43 were mild, 33 were moderate and 16 were severe, 78 per cent had pain or allied abnormal sensation in the chest (exclusive of the desire to cough), 50.8 per cent had cough or a desire to cough, and 12.1 per cent had dyspnea. We observed a preponderance of cough without pain among incipient cases, of pain without cough among moderate cases and an equal division of pain with and without cough among severe cases.

The subjects used various terms to describe the pain or allied abnormal sensation in the chest (exclusive of the desire to cough), in order of frequency, these were

Description	No. Cases
"Pain" (unqualified)	34
"Irritation"	17
"Rawness"	11
"Burning"	9
"Constriction"	9
"Like breathing cold air"	6
"Dryness"	5
"Pressure"	3
"Aching"	2
"As after running a race"	2
"Soreness"	1
"Sharp"	1
"Sick feeling"	1
"Fullness"	1
"Tickling" (no desire to cough)	1

In no case did incipient or mild chokes cause premature descent. Chokes caused descent in 25 instances, 13 of which were moderate and 12 of which were severe cases. Our policy was to remove subjects from the chamber when their chest symptoms became persistently uncomfortable. This accounts for the relatively large number of moderate rather than severe cases among those descending with chokes. If possible, the subjects were removed from the chamber before their chokes reached the severe stage.

The subjects in 77 cases of chokes rated their chest pain on a nine-point scale. Analysis of these scores revealed a progressively greater intensity of pain from incipient to severe cases.

Severity of Chokes	Average Intensity Score for Pain
Incipient	0.5°
Mild	1.5°
Moderate	2.5°
Severe	4.2°

There was no way for subjects to rate the intensity of their cough. Nevertheless, some knowledge of the intensity of cough could be gained from the interviews after descent. We devised a scale by which to rate its intensity from the description in the interviews.

Cough Intensity	Description
0°	No cough and no desire to cough at altitude or during descent
1°	Onset of cough during descent
2°	Desire to cough at altitude, but no cough even with deep breathing or after exercise
3°	Cough with deep breathing or after exercise at altitude, no cough at rest with ordinary breathing
4°	Cough with ordinary breathing at altitude, intensified with deep breathing or after exercise, no cough with shallow breathing
5°	Cough with ordinary breathing at altitude, intensified with deep breathing or after exercise, but not entirely relieved by shallow breathing
6°	Uncontrollable cough

By this scale the intensity of cough could be rated in 78 cases. Analysis of the scores revealed no steady progression of intensity as observed for pain.

Severity of Chokes	Average Intensity Score for Cough
Incipient	1.0°
Mild	0.6°
Moderate	2.2°
Severe	1.2°

In general, moderate and severe cases showed a greater intensity of cough than incipient and mild cases, one would expect this to be true by definition of each category of chokes. It is to be remembered that assignment of a case of chokes to one category or another depended on clinical judgment—the assessment of pain, cough and dyspnea. From analysis of scores, it would appear that pain is most important in judging the severity of chokes. Since pain does not appear in every case, consideration must be given to cough and

dyspnea We did observe the rare example of severe chokes with uncontrollable cough, but no pain

Under the conditions of our experiments, there appeared to be a significant though low degree of association between chokes and joint pain

TABLE II  
The Association of Chokes and Joint Pain and the Relation of Time of Onset of Chokes and Joint Pain

	Altitude	Frequency of Exercise	Preoxygenation Time in Minutes	No Chokes, No Joint Pain	No Chokes, Joint Pain	Chokes, No Joint Pain	Chokes, Joint Pain	Chi square	Association Coefficient Phi
Association of chokes and joint pain	38,000	2½'	0	11	43	1	35	4.4	0.22
	38,000	5'	0	40	52	5	39	12.7	0.30
	33,750	5'	0	30	44	1	19	7.5	0.28
	Altitude	Frequency of Exercise	Preoxygenation Time in Minutes	Chokes before Joint Pain	Chokes with Joint Pain	Chokes after Joint Pain	Total		
Relation of time of onset of chokes and joint pain	38,000	2½' & 5'	0	7	3	31	41		
	33,750	5'	0	2	3	10	15		
	30,000	2½' & 5'	0	0	0	5	5		
	38,000	5'	12, 51 & 111	2	0	10	12		
	Total Chi-square			11	6	56 28.3	73		

Note Allowing 1° of freedom, a chi-square of 3.80 is significant at the 5 per cent level, 5.4 at the 2 per cent level, and 6.6 at the 1 per cent level. The association coefficient, phi, is a type of correlation coefficient derived from chi square and expresses the degree of relationship independent of the number of cases. It ranges from zero to unity and is calculated  $\phi^2 = \chi^2/N$ .

The part of the table dealing with time relationships excludes incipient cases of chokes because 17 appeared during descent and would necessarily follow the onset of joint pain.

(table 2) Subjects who had chokes were also apt to have joint pain. Furthermore, subjects with both chest and joint symptoms tended to get chest symptoms after joint pains had appeared at altitude (table 2). We were

TABLE III  
Repetition of Chokes during a Subsequent Flight

Altitude	Frequency of Exercise	First Flight	Second Flight		Chi square	Association Coefficient Phi
			With Chokes	Without Chokes		
38,000	2½'	With chokes Without chokes	10 9	7 19	2.1	0.21
38,000	5'	With chokes Without chokes	11 7	15 35	4.2	0.25
33,750	5'	With chokes Without chokes	7 4	2 34	15.6	0.58

able to demonstrate a significant tendency for chokes to appear during the second flight if they had already appeared in the first flight in the experiment at 33,750 feet (table 3) No significant tendency for chokes to reappear during the second run was demonstrable in the experiments carried out at 38,000 feet The number of cases occurring in the preoxygenation experiments and those at 30,000 feet were too few to justify analysis

### INFLUENCE OF CERTAIN FACTORS ON CHOKES

*Altitude and Exercise at Altitude* Increasing the altitude produced a large difference in the intensity of chest pain, whereas increasing the exercise did not alter the severity of chest symptoms The frequency distribution of scores for intensity of chest pain in subjects with chokes at different altitudes and varying amounts of exercise at altitude are given in table 4

TABLE IV

Frequency Distribution of Scores for Chest Pain in Studies with Altitude and Exercise as Variables, Statistical Evaluation of Differences Produced by Altitude and by Exercise

Altitude				38 000	38 000	30 000	30 000
Frequency of Exercise				2½'	5'	2½'	5'
Intensity of chest pain				5	6	2	—
				2	4	3	3
				6	5	—	—
				7	—	—	—
				3	1	—	—
				1	3	—	—
				1	1	—	—
Experiments Compared				Average Difference of Intensity Scores		Critical Ratios	Statistical Significance
Altitude	Ex	Altitude	Ex				
30,000	5'	38,000	5'	0 95	1 34	2 14	Probable
30,000	2½'	38,000	2½'	1 72		4 24	Definite
38,000	2½'	38,000	5'	0 37	0 02	0 67	None
30,000	2½'	30,000	5'	0 40		1 63	None

*Note* Subjects with a score of zero were said to have had no pain according to the interview after descent The subjects used a nine-point scale by which to rate pain, but none recorded chest pain in excess of six degrees

We observed no case of moderate or severe chokes in the experiments carried out at 30,000 feet Furthermore, the total incidence of chokes at 30,000 feet was much less than at 38,000 (figure 1) We have already pointed out that the intensity of pain became progressively greater from incipient to severe chokes In general then, the intensity score for chest pain might be considered an index of the severity of chokes In terms of

intensity scores for pain, the more severe chokes appeared at the higher altitudes, whereas increasing the exercise done at a given altitude did not increase the severity of chokes

*Severity of the Chamber Test* If the use of oxygen and the rate of ascent are kept constant, two factors will influence the severity of tests in a de-

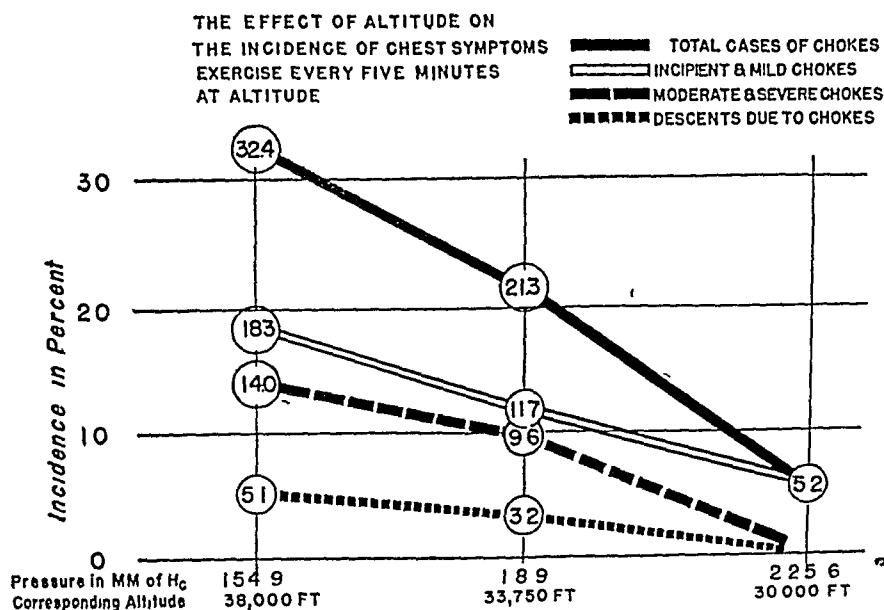


FIG 1

compression chamber (a) altitude, and (b) the amount of exercise performed at altitude. A test at a higher altitude with more exercise is more severe than one at a lower altitude with less exercise. The larger number

TABLE V  
Relation of the Occurrence of Chokes to the Time of Day

Altitude	38 000	38 000	33 750	30 000	30 000	Total
Frequency of Exercise	2½'	5'	5'	2½'	5'	
Flights						
With chokes in a m	11	16	12	4	3	46
Without chokes in a m	18	15	38	25	14	110
With chokes in p m	25	28	8	4	3	68
Without chokes in p m	36	77	36	67	96	312
Chi-square	0.0	5.5	0.3	0.95	3.3	8.65
Association coefficient, phi	0.00	0.20	0.05	0.10	0.17	0.12

of descents with the former test reflects its greater severity. Using the per cent of descents due to joint pain and chokes as a measure of the severity of the chamber test, one may deduce the following from figure 2

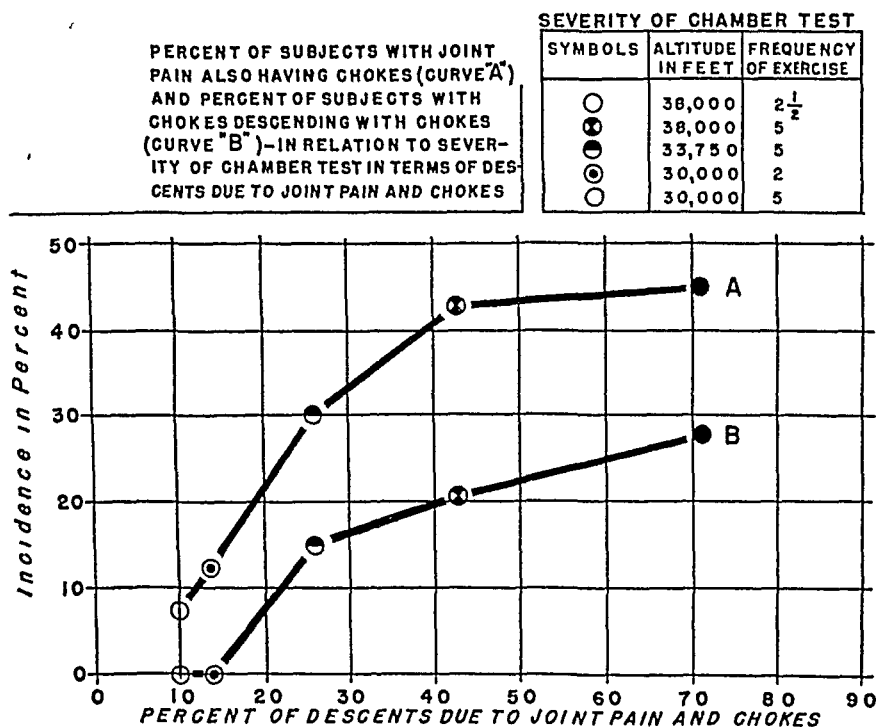


FIG 2 Severity of chamber test

*Note* In the table of symbols in figure 2, the open circle identifying data at 38,000 ft with the 2½ minute exercise is in error, the correct symbol is a completely filled circle. The 30,000, 2 minute entry should read 30,000, 2½ minutes

*a* As the severity of the chamber test increases, the percentage incidence of chokes among individuals who have joint pain is increased (Curve A)

*b* As the severity of the chamber test increases, the percentage incidence of descents caused by chokes among subjects who have chokes is increased (Curve B)

*c* As the severity of the chamber test increases, the above curves reflect a "law of diminishing returns," i.e., the curves tend to level off

*Time of Day* In general, there was no definite tendency for chokes to occur more frequently in the morning than in the afternoon (table 5). Chi-square for each of five series of experiments showed no significant relationship between the occurrence of chokes and the time of day. The series done at 38,000 feet with exercise every five minutes showed a probably significant tendency for chokes to occur more frequently in the morning. Chi-square for the totality of chokes among all five series indicated a significant tendency for chokes to occur more frequently in the morning, but the effect was small.

*Age* Among 268 subjects, the mean age of those making flights with chokes was the same as those making flights without chokes, 19.4 years. Hence, age did not influence the incidence of chokes in these experiments.

The 61 subjects used in the preoxygenation studies were excluded from this analysis because of the difference in experimental conditions. Our subjects ranged only from 17 to 24 years. It is possible that subjects in an older age group would show a higher incidence of chokes.

Armstrong<sup>1</sup> has recorded the popular theory on the etiology of chokes: the arrest of gas emboli in venous blood by the pulmonary capillary bed. The blockage results in discomfort in the chest, pulmonary edema, and unproductive cough at altitude. This may or may not be an adequate theory.

The serious and incapacitating nature of this syndrome was vividly impressed upon us when we had the opportunity of observing decompression sickness among a group of young men flying in an airplane at 35,000 feet.<sup>2</sup> The following describes the severest case of chokes we have observed, it occurred on one of the airplane flights.

#### CASE REPORT

G. D. K., age 21 (classified as susceptible to bends in the decompression chamber), developed mild bends while performing the standard five-minute exercise shortly after the airplane reached 35,000 feet. After nine exercises he suddenly developed a severe cough and became extremely pale. He failed to answer questions and his cough became more violent. Forty-three minutes after reaching 35,000 feet, the plane was sent into a fast dive, because the subject was semicomatose. When his mask was removed at 12,000 feet, his color was ashen, his face was covered with perspiration, and he did not respond to questioning until ten minutes later when he regained full consciousness at about 10,000 feet. The cough continued for one-half hour after reaching the ground. He was taken to the hospital and given supportive treatment. Three hours after the plane landed, he developed a severe frontal headache which lasted for eight hours. Thereafter, he was symptom free and completely well. In summary, this young man had severe chokes manifested by constant severe cough and accompanied by vasomotor collapse with moderate shock. We wonder whether many such severe cases of chokes might not be observed in the decompression chamber, if subjects with chokes were not removed early from the chamber.

#### SUMMARY

1 Chokes, a respiratory manifestation of aeroembolism at high altitude, are characterized by three major symptoms: chest pain, cough, and dyspnea.

2 A series of 132 cases of chokes, occurring in a group of experiments carried out in a decompression chamber with altitude and exercise as variables, was divided into four categories: incipient (40 cases), mild (43 cases), moderate (33 cases) and severe (16 cases). Among the latter two categories, chokes caused premature descent from the chamber in 25 instances.

3 Subjects who had chokes showed a slight tendency to have joint pain, also. The onset of chokes tended to occur after the onset of joint pain.

4 Increasing the altitude resulted in a significant increase in the incidence of cases having intense chest pain. Increasing the exercise done at altitude had no comparable effect. If the intensity of chest pain is accepted as an

index of the severity of chokes, then higher altitude resulted in more cases of moderate and severe chokes, whereas doing more exercise at altitude had no significant effect

5 As the severity of the chamber test was increased, chokes became more common in relation to the incidence of joint pain, and the descents due to chokes increased in relation to the incidence of chokes

6 Chokes occurred with approximately the same frequency in the morning as they did in the afternoon

7 The mean age of subjects who developed chokes was identical with that of subjects having no chokes 19.4 years

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- 3 Unpublished observations



# PRIMARY ATYPICAL PNEUMONIA. A CRITICAL ANALYSIS OF 500 CASES<sup>1</sup>

By SAUL KARPEL, Captain, M C , A U S , IRVING M WAGGONER, Lt Col, M C , A U S , and OSWALD S McCOWN, JR , Captain, M C , A U S .

DURING the past few years much has been written concerning non-bacterial pneumonia. This type of pneumonia has been and still is called by various names. Acute diffuse bronchiolitis, acute interstitial pneumonitis, primary atypical pneumonia, acute pneumonitis, bronchopneumonia, influenzal pneumonitis, disseminated focal pneumonia and benign bronchopulmonary inflammation are designations that have been used.

Previous reports of primary atypical pneumonia have been issued, almost without exception, from army hospitals, colleges and health departments, in all instances where roentgen-ray facilities were available, usually at no cost to the patient, and the chest film was obtained as a part of the routine examination. This point is stressed, as it is our opinion that the infection is present in many cases which remain undiagnosed unless roentgen-ray facilities are available and used frequently.

Becoming "primary atypical pneumonia-conscious" is another important factor in discovering and diagnosing the condition. Our entire hospital staff became "pneumonia-conscious" and this undoubtedly resulted in the earlier detection of a greater number of cases.

TABLE I\*  
Age—Years

No Cases	1-10 years		10-20 years		20-30 years		30-40 years		40-50 years	
	No	%	No	%	No	%	No	%	No	%
500	8	1.6	20	4.0	290	58.0	139	27.8	43	8.6

\* This table, and those following are shown to denote the number and percentage of each physical finding, based on the investigation of 500 cases of primary atypical pneumonia studied at the Station Hospital, New Orleans Port of Embarkation, New Orleans, Louisiana.

*Etiology* The cause of the disease has not been definitely established. No special studies to determine the causative factor were undertaken by us.

*Incidence* Little is known concerning the incidence of primary atypical pneumonia. The analysis of total admissions to this hospital and total admissions to the medical service alone, demonstrates the incidence experienced by us. Approximately 700 cases of primary atypical pneumonia have

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From the Medical Service, Station Hospital, New Orleans Port of Embarkation, New Orleans, Louisiana, May, 1944.

been diagnosed out of 7,000 admissions to the medical service during the time interval analyzed

*Onset* The onset of the disease in the majority of cases is insidious. An analysis of symptoms at onset is presented in table 2. The patient feels that he is developing a common cold, and many patients will not seek medical aid for days or weeks. We are convinced that many of those developing the benign type of disease never report at sick call or are attended by a medical officer. The more usual initial symptoms of those developing a moderately severe infection will be in the order mentioned: malaise, chilliness, headaches, rhinitis, sore throat and cough, accompanied by substernal

TABLE II  
Symptoms

No Cases	Acute		Insidious		Chill		Chilliness		Cough		Productive		Non Productive		Substernal Pain		Pleural Pain		Abdominal Pain	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
500	129	25.8	356	71.4	14	2.8	218	43.6	345	69	222	44.4	119	23.8	99	19.8	52	10.4	22	4.4

pain or heaviness. The complaint of substernal pain or heaviness in the chest, we believe, was largely the result of the muscular action entailed by excessive cough. In slightly more than 10 per cent, the chest pain was classified as pleural pain. In these the pain was unilateral, associated with respiration and cough, and of the "catching" character typical of pleuritic involvement. In a lesser number of cases the onset is acute with the aforementioned symptoms developing in a period of 24 hours or less. In an even smaller number the infection is ushered in with a shaking chill and quickly developing prostration. In the average case the cough was severe and productive in most cases of a tenacious mucoid sputum. Blood streaking of the sputum was relatively common in our series. After a few days the sputum usually changed to the mucopurulent type.

The temperature, in the usual case, became elevated and ranged from 102° F to 104° F. The fever was of a septic type with an afternoon and night rise to the previously mentioned figures and a fall to normal or nearly so by morning. The duration of fever is shown in table 3. Over one-half of the patients remained febrile for four days. Usually patients appearing alarmingly ill during the night appeared reassuringly well when seen the next morning. It may be noted in table 3 that certain of the benign infections were completely asymptomatic.

*Physical Findings* The physical findings were remarkable in many respects. The findings most frequently present, in their respective incidence, are presented in table 4. The most constant physical finding was râles, which were present at the time of the first examination in approximately one-half of our cases. By far the largest number were of the "wet" variety

TABLE III  
Fever Duration—Days

No Cases	0 days		1-4 days		5-9 days		10-14 days		over 14 days	
	No	%	No	%	No	%	No	%	No	%
500	52	10.6	279	55.8	141	28.2	18	3.6	9	1.8

TABLE IV  
Physical Signs

No Cases	Impaired Percussion		Harsh Breath Sounds		Suppressed Breath Sounds		Râles	
	No	%	No	%	No	%	No	%
500	125	25.0	83	16.6	93	18.6	269	53.8

(298 patients received chemotherapy)

Moist, crepitant râles were the usual type, but in those cases with severe or extensive involvement bubbling râles were a frequent finding. Less often we encountered the dry, piping or musical râles usually associated with the bronchial spasm of asthma. Percussion impairment was not noted in a majority of the cases, and the absolute dullness so characteristic of lobar pneumonia was rarely present.

In about 4 per cent of our series, abdominal pain was the chief complaint. A number of these presented the classical picture of acute appendicitis. In a few the picture was so convincing that appendectomy was performed in full knowledge of the presence of respiratory infection. The appendix, in each case, was normal. Our observations have led us to believe that the abdominal syndrome occurred in those cases in which the pneumonic infiltration in the lung came in close proximity to the diaphragm. A few cases presented abdominal pain which simulated renal disease and a very few focused attention on the liver.

The physical findings were bizarre in many instances. Breath sound changes resulted in our medical officers incriminating one lung when, in many cases, the roentgen-ray disclosed the pneumonic infiltration to be in the opposite lung. The explanation of this error is obvious. Reference to table 4 discloses that the breath sound changes, when present, are unpredictable and unreliable. Increased, or as we have termed them, harsh breath sounds and suppressed breath sounds occur with almost equal frequency.

A few unusual features are worthy of mention. We estimate that approximately 10 per cent of our series presented no abnormal physical findings. Some of this group were very ill and some fell into the completely asymptomatic group. The asymptomatic cases have resulted in several

amusing incidents. It has been our experience to discover the presence of primary atypical pneumonia in the course of routine chest films in soldiers applying for Officer Candidate School, who later developed symptoms. One diagnosis came as a result of a misunderstanding in the roentgen-ray department. A roentgen-ray of the lumbosacral area had been requested, but the technician substituted the chest and a report of a pneumonic infiltration was submitted. A striking example of a completely asymptomatic case was found when a soldier was routinely roentgen-rayed in an out-patient clinic. The roentgenologist reported the presence of pneumonia. A request that the soldier be instructed to return to the hospital for admission was made. The soldier was found actively participating in a ball game and was completely bewildered when told that he was to return to the hospital. Equally bewildered was the ward officer as he received a patient with no complaints or physical findings.

The almost complete absence of cyanosis, dyspnea and abdominal distention deserves mention in contradistinction to the frequency of these findings in lobar pneumonia, especially prior to the introduction and use of the sulfonamide drugs.

TABLE V

No. Cases	Left Lower		Right Lower		Left Upper		Right Middle		Right Upper		2 Lobes		3 Lobes		4 Lobes		5 Lobes	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
500	198	39.6	264	52.8	31	6.2	58	11.6	47	9.4	111	22.2	11	2.2	0	0	2	1.0

*Roentgen-Ray Findings* In this report no case has been included which lacked roentgen-ray confirmation. As previously noted, many cases will escape detection unless roentgen-ray facilities are freely used. It was common in our experience to have the first chest film show increased markings or increased peritruncal shadows compatible with a respiratory infection. Subsequent films, after 24 to 48 hours, then registered the pneumonic infiltration. The characteristic finding on the film is a soft shadow radiating from the bronchial trunk. Involvement of an entire lobe may occur, but in the typical case the involvement is limited to a portion of a lobe or lobes. The density of the shadow and complete lobar involvement seen in true lobar pneumonia were infrequently observed in this series. The chest film was diagnostic, not only of pneumonia, but of atypical pneumonia in most cases.

Reference to table 5 indicates the preponderant occurrence of the infection in the lower lobes. In 52.8 per cent the involvement was in the right lower lobe. The left lower lobe was the site in 39.6 per cent, right middle lobe in 11.6 per cent, right upper lobe in 9.4 per cent, and left upper lobe in 6.2 per cent. In 22.2 per cent two lobes were involved, in 2.2 per cent

three lobes and in 1 per cent all lobes were involved. Curiously enough, in none of our series did we find four lobe involvement.

In two or three cases, we have had roentgen-ray evidence of a pneumonic infiltration several days before the development of symptoms of illness. The reverse was true in one unusual case. This patient's temperature rose to 103° to 105° F daily for six days, but frequently repeated chest films were negative until the seventh day when a pneumonic process became evident.

In the majority of cases, resolution of the pneumonic process was observed by repeated roentgen-ray examinations. Table 6 records the aver-

TABLE VI  
Resolution—Days

No Cases	1-10 days		10-20 days		20-30 days		30-40 days		40-70 days	
	No	%	No	%	No	%	No	%	No	%
500	197	39.4	175	35	62	12.4	60	12	6	1.2

age number of days necessary for resolution. Although presented as an average, we do not offer the figure as a guide as we have noted the clearing of a pneumonic process in as little as two days and, conversely, have noted the persistence of the process for as long as 60 days.

*Laboratory Findings.* Analysis of the blood cell counts discloses that in 56.6 per cent of the cases the leukocyte count was within normal limits. We have arbitrarily taken 5,000 as the lowest number and 10,000 as the highest number considered within normal range. Slightly more than one-fourth had leukocytosis. Usually moderate, the leukocytosis not infrequently reached twenty and thirty thousand. In 6 per cent leukopenia was present. In 35.4 per cent young forms were noted in the differential count. In 18.4 per cent of the cases study of the blood film revealed increased eosinophilic cells. This finding was noted more often in counts performed later in the course of the illness, and we are at a loss to account for the manifestation. Is it a response to the infecting agent, an immune reaction, or does sulfonamide administration enter in? Excluded from our figures of eosinophilia were patients with parasitic infestations. Well over 100 blood cultures were done before we discontinued this laboratory procedure. All were negative.

Reference to table 7 shows that approximately one-half the cases had sputum examinations. This number represents but a small proportion of sputum examinations done, as in many cases sputum examination was repeated from two to eight times. Early in the illness, the sputum is a tenacious mucus, frequently blood streaked. After a few days, the sputum becomes mucopurulent. Laboratory examinations of the sputum were of no aid. In about 2 per cent of our cases a type-specific pneumococcus was reported. In all instances we believe this was an incidental finding and the

organism present was not the causative agent. The usual report was "no pneumococci present," or in a moderate number of cases, "pneumococci present but too few for typing."

Albuminuria was noted in about 10 per cent of our cases and microscopic hematuria in 4 per cent. These findings appeared almost entirely in patients receiving sulfonamide medication, and we believe they are the result of renal irritation from the drug.

TABLE VII

Laboratory

No. Cases	Leukopenia		Normal		Leukocytosis		Eosinophilia		Sputum Exam		Blood Cultures		Albuminuria		Hematuria		Young Forms (Blood)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
500	30	6	293	56.6	152	30.4	92	18.4	245	49	141	28.2	49	9.8	20	4.0	177	35.4

*Complications* Less than 3 per cent of the patients in the entire series developed complications. Whether sulfonamide administration reduced the incidence of complications we do not know. We doubt that it did. The pathologic lesions of the disease would seem to provide a fertile field for the development of secondary infection. Apparently it does not.

Pleurisy with effusion occurred in four cases. Absorption of the fluid and complete recovery took place spontaneously. In two cases lung abscess developed. Both cases were maintained on sulfonamide medication and one healed completely in the surprisingly short period of one month and the other in three months. It was observed that the sputum in both cases soon assumed a nonpurulent appearance and never developed the foul odor so common in this condition. One case developed an interlobar empyema. The patient's course was febrile, in spite of sulfonamides, for several months and then the temperature returned to normal and the last film showed almost complete absorption of the process.

Bronchiectasis was found to be present in almost 2 per cent of the cases. This finding has proved to be one of great interest and has aroused numerous questions. We have been unable to determine whether the bronchiectasis preceded the pneumonic process or not. We have a strong suspicion that an acute bronchiectasis may develop with the infection. Certainly these patients gave no history of previous cough, productive or nonproductive, and it must be assumed that the induction chest film was negative. It may be that the ease, both to patient and physician, with which the bronchogram can now be made, will result in a greater use of the procedure which will clarify the matter. It is very possible that early and minimal bronchiectatic changes, not detectable on the routine chest film, are much more common than we presently believe.

In connection with bronchiectasis, we have speculated about the possibility that the changes may be reversible, especially in the cases of acute bronchiectasis, if such exist. A most lamentable fact is the impossibility of follow-up in our cases. Certain of the patients suffer a persistent cough, which eventually becomes nonproductive. Several months may elapse before the cough disappears entirely.

A marked asthenia has been observed to follow the infection in a few cases. It is possible that this manifestation is the result of sulfonamide medication. No complication in the entire series necessitated any surgical procedure.

*Differential Diagnosis* The common respiratory diseases are, by far, the most important factors to be considered in differential diagnosis. As previously noted, the onset of the disease seems to differ little from that of the common cold, or grippe. Without roentgen-ray examination there is no doubt that many cases are termed a "chest cold" or bronchitis, and the presence of the pneumonic process remains unknown. Differentiating atypical pneumonia from lobar (pneumococcic) pneumonia is, except in rare instances, not difficult. The onset of atypical pneumonia is usually insidious and without a chill as opposed to the abrupt onset with chill in lobar (pneumococcic) pneumonia. Fever is not so marked and not sustained at a constant level as in lobar (pneumococcic) pneumonia. Dyspnea and cyanosis are usually not present in atypical pneumonia. Sputum is mucoid or mucopurulent, not rusty. The normal number of leukocytes, negative sputum and blood culture, lack of physical signs of consolidation, typical roentgen-ray appearance, and lack of response to sulfonamide medication which characterize atypical pneumonia are further differentiating factors.

Our roentgen-ray staff has diagnosed tuberculosis in a few cases in which involvement was limited to one or both upper lobes. Subsequent films showing resolution of the processes resulted in corrected diagnoses.

A word of caution is inserted to avoid unnecessary surgical procedures in those cases presenting the clinical picture of acute appendicitis. Where appendicitis cannot be definitely ruled out we must, of course, resort to operation.

Differentiation from renal disease and disease of the liver is rarely necessary.

*Prognosis* The mortality in this series was but 0.2 per cent. Cases could have been added to lower this figure. It is evident, therefore, that the prognosis is excellent. The low incidence of complications, excepting the cases of bronchiectasis, and the fact that none required surgery but instead cleared spontaneously, indicates that complete recovery is the rule.

In table 8 is listed the average number of hospital days for the patient. This figure is not comparable to hospital days in civilian institutions. It must be borne in mind that the army hospital serves not only as a hospital

for the acute illness, but also as a convalescent institution. Soldiers, upon discharge from the hospital, must be physically fit for return to duty. In civilian life many of our cases would not have required hospitalization and others would have needed but a short hospitalization period.

TABLE VIII  
Hospital Days

No Cases	4-15 days		16-30 days		31-45 days		46-60 days		over 60 days	
	No	%	No	%	No	%	No	%	No	%
500	161	32.2	277	55.4	45	9.0	12	2.4	5	1.0

*Treatment* There is no specific treatment available. Those general measures usually employed in treating systemic infections were used. Bed rest is important and essential. Adequate fluid intake must be assured, and this requires considerable nursing care, the importance of which cannot be minimized.

Symptomatic treatment, such as the use of the common antipyretics and non-narcotic analgesics for headache, slight pleural pains and other minor aches and pains, was freely used. Opiates, usually codeine, were used for more severe pain and incessant cough. In those patients considered seriously ill, the oxygen tent was used at the first sign of dyspnea or cyanosis. In our experience small transfusions of whole blood have been of definite benefit. When possible, the donor chosen was an individual who had recovered from the disease.

In more than half of the present series, sulfonamide drugs were administered. Practically all of the cases considered seriously ill received sulfonamides and the remainder of those receiving the drug, although not considered seriously ill, usually had a rather marked fever. In approximately half the cases, sulfathiazole was used and in the other half sulfadiazine was given. Sulfanilamide and sulfapyridine were given in but a few cases. The initial dose varied from two to four grams, and the drug was continued on a four hour schedule supplying six grams per day. The usual blood levels were obtained. In those patients receiving sulfonamide medication, the average amount given was 30 grams.

We are thoroughly convinced of the complete ineffectiveness of the sulfonamides in this infection. We have repeatedly observed progression of the pneumonic process in the presence of therapeutic blood levels of the drugs.

Although not used by us, there are two therapeutic measures which may be of value in the critically ill patient. One is the administration of oxygen under pressure, and the other is postural drainage. To one who has inspected the lungs of a patient dying from the disease and noted the flooded



condition of the lungs, postural drainage would certainly seem worthy of trial.

It seems proper to note here that, of the cases receiving sulfonamide medication, none suffered a serious toxic reaction. As noted before, a number manifested renal irritation by the appearance of albuminuria and microscopic hematuria. We presume we have had the usual amount of nausea and vomiting and skin rashes. Withdrawal of the drug was the only measure required in such cases. The entire absence of serious toxic reactions is attributed to the fact that in all cases careful attention was given to assure an adequate fluid intake and urinary output.

#### CASE REPORT

The patient, white, age 40, was admitted acutely ill with a nonproductive cough, fever and generalized aching on day of admission. Family and previous personal history were irrelevant. Initial examination disclosed the temperature 102° F, pulse 100, respiratory rate 22, blood pressure 114 mm Hg systolic and 60 mm diastolic. There were harsh breath sounds and coarse expiratory rales over the entire chest, more marked on the right. There was a moderate leukopenia and on the third day a type 15 pneumococcus was isolated from the sputum. Roentgen-ray examination disclosed a patchy, diffuse infiltration throughout the right lung field. The roentgen-ray diagnosis was primary, atypical pneumonia with tuberculosis a possibility. Seven days later, another roentgen-ray examination showed clearing of the processes in the right upper and lower lobes.

The course was satisfactory, the physical signs became much less prominent and there was roentgen-ray evidence of resolution of the pneumonic process. The temperature fell to normal on the fourth day and remained so for 48 hours. On the sixth day, the temperature suddenly rose to 101° F, but rapidly returned to normal. On the eighth day, dyspnea and right lower chest pain developed and simultaneously the temperature rose to 104° F. Physical signs indicated involvement of the entire right lung and lower lobe of the left lung. The patient appeared critically ill. Oxygen administration was ineffective. The patient became progressively worse and death occurred on the fourteenth day. Clinically, the immediate cause of death seemed to be an anoxemia.

*Autopsy*\* Gross Findings The lungs were voluminous, crepitant and spotty. There were irregular nodules, primarily in the right lung and to a lesser extent in the left upper lobe. These had a firm consistency, but not that of consolidated lung. The visceral pleura of the left lung was smooth and glistening, except for areas of fibrinous and membranous adhesions. The cut surface of the left lung revealed dark red, hemorrhagic areas, which had an increased density. There were also fleshy, red areas of collapse mingled with yellow, feathery lung tissue. The pleura of the right lung was a mottled blue and gray. The dark blue collapsed areas were depressed and often surrounded by bullae of sub-pleural emphysema. There were numerous bands of early, organizing membranous adhesions which, on section, did not reveal any demonstrable blood vessels. On section, the upper and lower lobes of the right lung revealed numerous dark red, hemorrhagic areas of increased density, mingled with fleshy, bright red areas of collapse and yellowish, feathery emphysematous lung tissue. The lower trachea and the bronchi of both lungs were filled with thick, slimy secretions, the hilar lymph nodes were large and succulent.

\* Autopsy by Major Alexander Kushner, M.C.

**Bacteriological Findings** Direct smear and culture of bronchial secretion showed a few pneumococci present. Direct smears of various portions of the lung parenchyma proper showed no bacteria present and gave no growth. Culture of the heart blood gave no growth.

**Microscopic Findings** The interstitial tissue of the upper lobe of the right lung including the alveolar septa was thickened and infiltrated primarily with mononuclear cells. A rare, pyknotic, polymorphonuclear cell was seen. There were numerous large phagocytes laden with blood pigment. No fibrin was seen. Some of the alveoli were empty and were the seat of a compensatory emphysema. An occasional large bronchus was partially filled with mucopurulent exudate. There was also an acute pleuritis with mononuclears predominating. The examination of other lung areas corresponded.

### SUMMARY

A detailed analysis of 500 cases of primary, atypical pneumonia has been presented. The insidious nature of the disease, variable physical signs, and difficulty in diagnosis without roentgen-ray examination were stressed. Certain of the cases were asymptomatic. Caution was advised in connection with the cases simulating acute appendicitis and a brief reference was made to the roentgen-ray findings, including sites of the pneumonic process and the time required for resolution. Under laboratory findings, the leukocyte level, incidence of early forms and eosinophilic cells, blood culture, sputum examination and urinary findings were listed. The low incidence of complications was noted. Differential diagnosis, prognosis and treatment were discussed, and the ineffectiveness of sulfonamide medication was noted. A brief case report of the single death in the series was appended, including that portion of the autopsy report dealing with the lungs. Further studies of this disease, especially efforts to determine the causative agents, are urgently needed.

### ADDENDA

This paper was originally submitted for publication in June, 1943. Owing to circumstances beyond our control it became necessary to resubmit it at this time. Since June, 1943 a number of excellent papers on the same subject have appeared in various medical publications. In some instances the findings of others have coincided to an amazing degree with those reported by us.

In the November, 1943 issue of *The Bulletin of the U. S. Army Medical Department*, Blades and Dugan in a paper titled "Pseudo Bronchiectasis Following Atypical Pneumonia" considered a problem suggested in our paper.

The continued high incidence of atypical pneumonia since our report was compiled emphasizes the importance of further studies and reports of the disease.

# CASE REPORTS

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## HEPATOLENTICULAR DEGENERATION (WILSON'S DISEASE), REPORT OF ONE CASE WITH SEVERE PORTAL CIRRHOSIS AND SPLENOMEGALY \*

By HARRY FREEDBERG, M D, *Salem, Massachusetts*

In 1912 Kinnier Wilson described a series of 13 cases of extrapyramidal disease associated with liver cirrhosis. His original description was as follows: "This disease which occurs chiefly in young people, often familial but not congenital or hereditary, is characterized by involuntary movements, dysarthria, muscular weakness, spasticity, contractures, progressive emaciation, mental deterioration and frequent emotional disturbances. This disease is progressive and, after a longer or shorter period, fatal." Since then sporadic cases have been reported in the literature.

Many hypotheses have been advanced as to the etiology of the disease and chief among the reviews has been that of Jervis. According to an early hypothesis, the brain lesions are primary and the liver damage is secondary to the involvement of certain vegetative centers in the hypothalamus. Another theory holds that the hepatic and cerebral lesions are not interdependent, but rather the result of the pathological agent acting at the same time in both the liver and lenticular nuclei. According to a third theory, the disorders of brain and liver are both expressions of an heredodegenerative or abiotrophic process. It has also been stated that an underlying constitutional anomaly of metabolism is responsible for the changes in both organs. A final theory and one that is most widely accepted since Wilson gave credence to it in his studies states that the liver is first affected and that the lenticular lesions follow as the result of the action of some unspecified toxin which either originates from, or is not neutralized by the damaged liver. Waggoner and Malmud report five cases of ordinarily acquired liver disorder showing cerebral changes, and compare these with two cases of Wilson's disease. They conclude that the involvement of the central nervous system in Wilson's disease must be regarded as secondary to that of the liver since it can be reproduced both clinically and anatomically in certain acquired liver diseases.

Liver function tests have been reported by Sweet in nine cases of this disease. He obtained conclusive evidence of hepatic dysfunction by various sensitive tests. The serum colloidal test of Gray, the prothrombin time and the bilirubin excretion tests were found to be more sensitive indicators of hepatic damage in cases of minimal cirrhosis of the liver than the galactose tolerance, bromsulphalein retention or hippuric acid tests. He found that plasma protein levels and the cholesterol ester partition were of little or no value in detecting hepatic disease in cases of hepatolenticular degeneration.

\* Received for publication September 13, 1943

Barnes and Huist have described individuals, in the families of cases of progressive lenticular degeneration, who developed cirrhosis of the liver and ascites, and died prior to the development of nervous manifestations

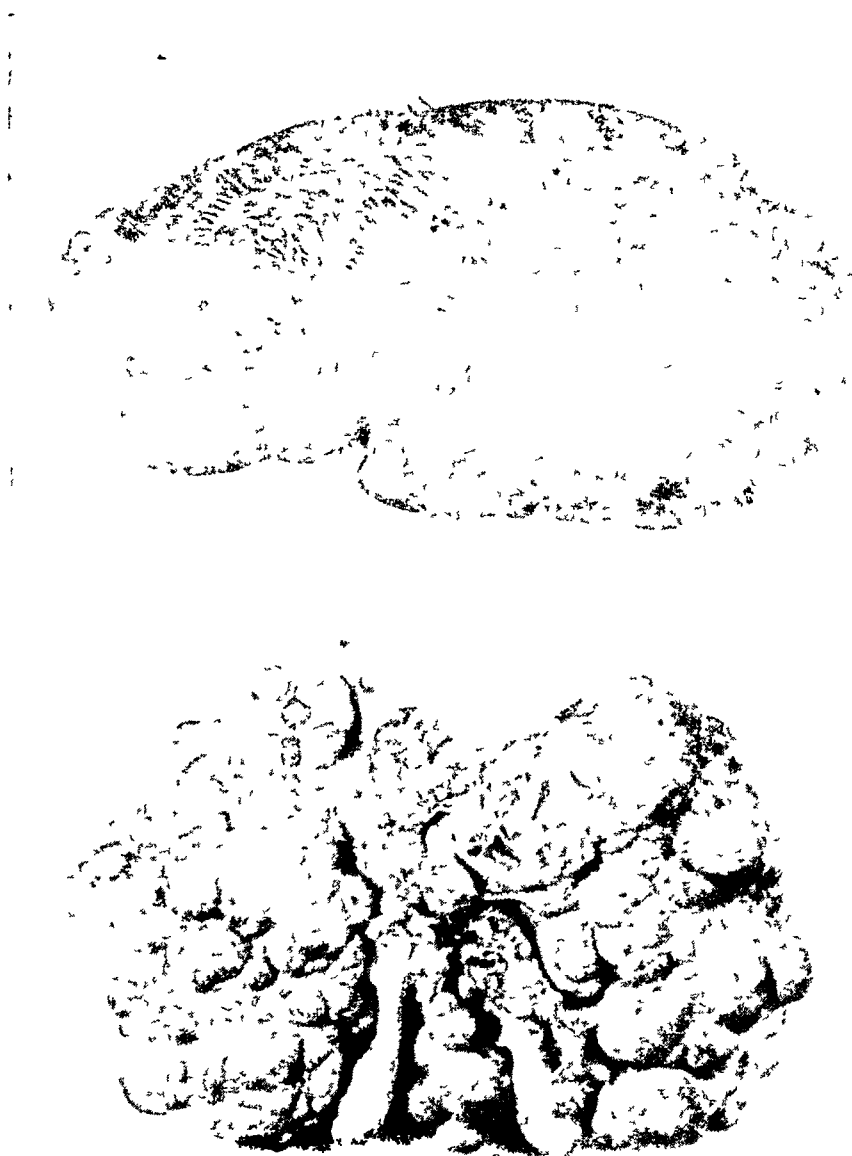


FIG 1 (above) The spleen (below) The liver *Credit Photo Salem Hospital*

In most of the cases reported in the literature, death has been attributed primarily to the cerebral involvement. Severe hepatic dysfunction with portal cirrhosis sufficient to produce clinical symptoms has been infrequently described. This case is being reported because of the severe portal cirrhosis with massive splenomegaly, and because of death being caused by a hemorrhage from a ruptured varix.

## CASE REPORT

A 20-year-old single, Italian female was first seen in 1935, and was closely followed until her death in 1941 with two admissions to Salem Hospital, and an intervening admission to the Piatt Diagnostic Hospital. She complained of marked nervousness, periods of amenorrhea, with coarse tremors of both hands. She adjusted quite well, with little progression of symptoms until five years later when she reported loss of approximately 25 pounds in weight, bleeding gums, increase in her nervousness and the development of an abdominal mass. She was first admitted to the Salem Hospital on June 20, 1940.



by Doris Lundgren 4/25/41

Credit Photo Salem Hospital

FIG 2 Cross section of the brain showing the diseased area

**Past History** The patient had had measles and mumps when under five years of age, without complications or sequelae. She always led a fairly restricted life, reached the eighth grade, but did not graduate from grammar school. The patient had always been handicapped by a speech impediment. She had abdominal pain from time to time over the left side of her abdomen, not associated with gastrointestinal symptoms. Her appetite was good and she never noticed tarry stools, nor coughed or vomited blood.

**Family History** The patient's father was living and well at 57, her mother had had a tumor of some kind and died of inflammation of the leg at 37. Three siblings were living and well. As far as it is known, there was no family history of neurological disorder or blood dyscrasia.

**Physical Examination** She was a small, fairly well nourished woman with ashen complexion. Her face was unattractive because of the prominence of her jaws and teeth which was so great that she was unable to close her lips, the gums were exposed, hypertrophied and bleeding. She was flat-chested. Breath sounds were resonant and vesicular throughout. There were no râles or other adventitious sounds. Heart sounds were regular and of good quality, rapid and regular, rate 144. Blood pressure was 124 mm Hg systolic and 66 mm diastolic. The heart was not enlarged. There were no murmurs. The abdomen was greatly protuberant and tense. A fluid wave and shifting dullness could be made out. The left side of the

abdomen was more prominent than the right, and in the left upper quadrant filling most of the left half of the abdomen there was a large, smooth, firm, slightly tender mass consistent with the spleen. The liver was not palpable and the liver dullness was entirely absent.

*Neurological Examination* The patient had a constant grin which remained relatively fixed. The speech was slow and monotonous, and there was some difficulty in swallowing. The slit-lamp examination showed no evidence of Kayser-Fleischer ring. Fundus examination was negative. The pupils reacted to light and accommodation, extraocular movements were normal, cranial nerves were intact. There were gross tremors of the head, protruded tongue, trunk, and tremors of the extended hands, which were increased with involuntary movement, especially on the left side. There was also a slight tremor of the legs. There was a Warner's hand on the left. The deep reflexes in the upper extremities were of the basal ganglia variety, that is, with each reflex there was imperfect relaxation. This was also true to a less extent in the lower extremities. Motor power was normal throughout. There was no spasticity, atrophy or fibrillary twitching. Romberg test was negative. Plantar responses were normal. There was no disturbance in sensation to pin-prick, brush or tuning fork.

Laboratory work performed at this hospital and at the Pratt Diagnostic Hospital, where she was also studied at a later date, showed the following findings.

*Roentgenographic Findings* Esophagus. There were extensive abnormalities, involving the whole length of the esophagus, consisting in tortuous defects of the mucous membrane, which changed in width with respiration. The findings were characteristic of extensive varicosities of the esophagus. Roentgenograms of the skull were negative. Anteroposterior views of the long bones of the arms and legs showed marked demineralization for a patient of this age, particularly in the cancellous portions, where in some areas it was almost cystic in appearance. Anteroposterior views of the abdomen revealed a large tongue-shaped shadow extending down from the left costal margin nearly to the crest of the ilium displacing gas-filled loops of the bowel to the right, and through it one could outline the left kidney. The left iliopectineal border was fairly clear.

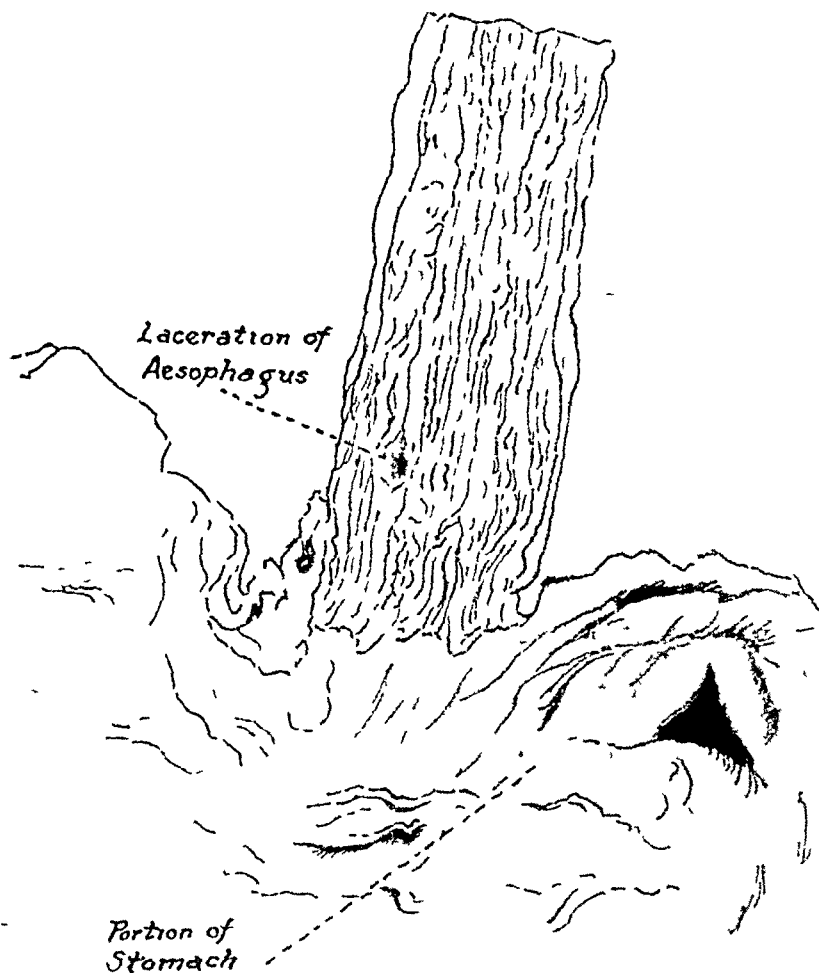
*Urine studies* were negative for Bence Jones protein and urobilinogen, and were otherwise unremarkable.

*Blood Studies* Blood platelets varied from 200,000 to 400,000. Red blood cell counts varied from 3,800,000 to 4,120,000. Hemoglobin was 51-64 per cent. Blood smears showed some cells well filled with hemoglobin, some showed marked achromia, there were a few elongated red cells, a few stippled cells, slight anisocytosis and poikilocytosis, and polychromatophilia, and 1-3 target cells. Reticulocytes numbered 2 per cent, the hematocrit reading was 34 per cent. Bleeding time was 3½ minutes, clotting time, seven minutes. The hypotonic fragility test showed a definite change in minimal resistance, complete hemolysis not being present until 12 concentration of sodium chloride. White blood cell count was 8,000, with 70 per cent polymorphonuclears, 15 per cent lymphocytes, 8 per cent monocytes, 6 per cent bands, 1 per cent eosinophiles. Blood sugar was 79 mg per cent, fasting.

*Serology* Hinton and Wassermann reactions were negative on two tests, Kahn reaction was positive on two tests. Blood sedimentation rate in one hour was 13 mm by the Westergren method.

*Liver Function Tests* The prothrombin time was 35 seconds, cholesterol 107 mg per cent total, free, 40 mg per cent, and esters 67 mg per cent. Bromsulphalein excretion test showed a retention of 50 per cent of the dye in an hour. Icteric index was 12. Blood bilirubin was 1.4 mg per cent total, blood phosphatase 60 Bodansky units per 100 cc. Blood serum proteins were 7.10 gm per cent, with 2.95 gm per cent albumin and 4.15 gm per cent globulin. The Takata-Ara test was positive in four tubes.

The patient's last admission to Salem Hospital was on April 14, 1941. She was readmitted with a complaint of hemorrhages from the mouth, associated with vomiting and tarry stools of several months' duration. She was acutely ill, pale and apprehensive. The abdomen was enlarged. The ankles were edematous. Pulse and respirations were rapid. Three days after admission abdominal paracentesis was



*By Doris Lundgren 4/35/41*

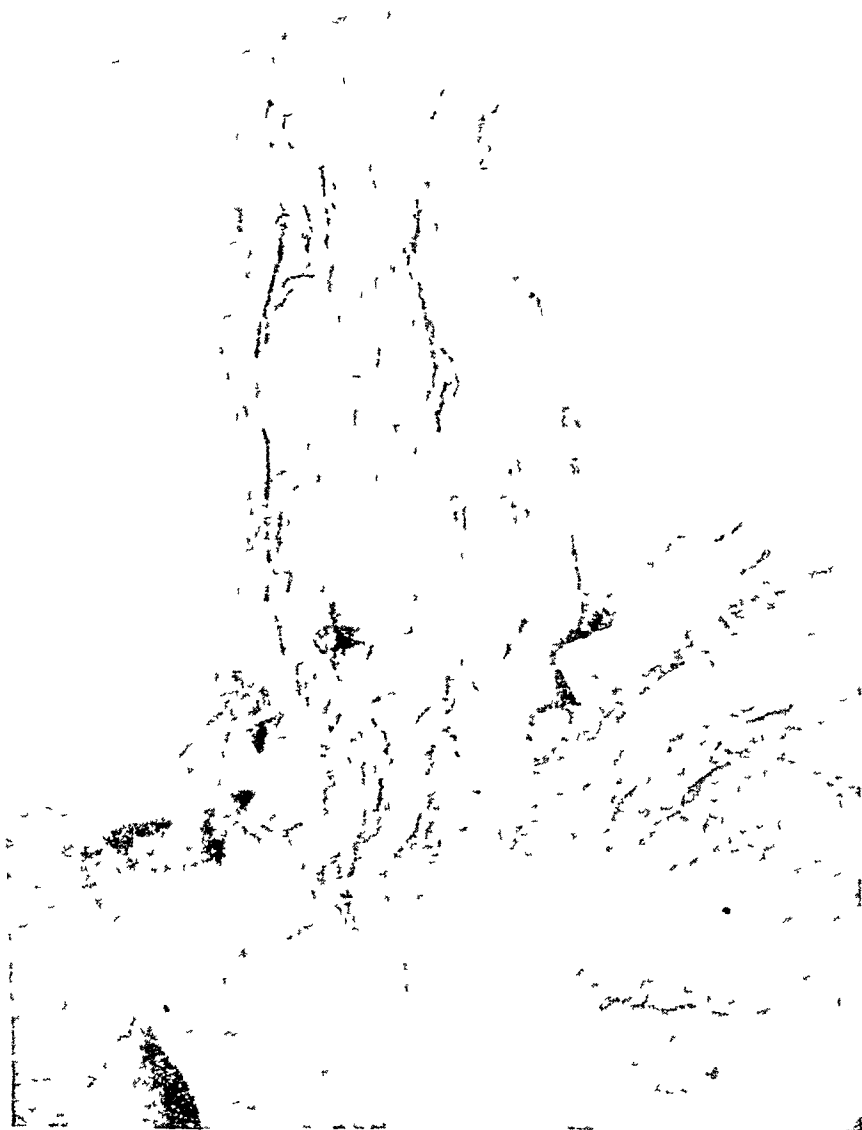
*Credit Photo Salem Hospital*

FIG 3 Laceration of esophagus

performed with the removal of four liters of light, straw-colored, transparent fluid of the consistency of water. She rapidly became moribund and died on the sixth hospital day, April 20, 1941.

*Autopsy Examination* Peritoneal cavity. The peritoneal cavity contained no adhesions. There were approximately two gallons of straw-colored fluid. The appendix was retrocecal and bound down. The mesenteric lymph nodes were

slightly enlarged and on gross section many of them were red and hemorrhagic. The diaphragm was at the fifth rib on the right and fifth interspace on the left. The viscera were in approximately normal position. There was no evidence of congenital malformation. Gastrointestinal tract. The esophagus was dissected out along its entire course and appeared to be distinctly enlarged and bluish gray in



*Credit Photo Salem Hospital*

FIG 4 Esophagus showing the perforation

color. Upon opening it at a point 5 cm above the cardiac junction, a small perforation of a varix could be seen measuring approximately 3 mm in diameter, out of which protruded a small thrombus. The esophagus when held up to the light showed numerous tortuous bluish red dilated veins. The stomach contained a large amount of brownish red bloody fluid. The stomach itself was entirely negative



The duodenum, jejunum, and ileum contained fresh blood but showed no morphological lesions. The entire large bowel was negative.

**Spleen** The spleen weighed 740 grams, was distinctly enlarged, and reached almost to the crest of the ilium. The capsule was not noticeably thickened and was slate grayish in color. The cut surface was dark red. Scraping yielded bloody pulp. Examination of the splenic vein and artery failed to reveal any thrombus. However, around this area several hemorrhagic lymph nodes were found. Microscopic sections of the spleen showed a moderate degree of fibrosis of the pulp and engorgement of the sinusoids, and the lymphoid tissue was not unusually hyperplastic.

**Liver** The liver weighed 675 grams, was small, firm, uniformly nodular. The average nodule measured approximately 2 cm in diameter. There were no adhesions between the upper surface of the liver and diaphragm. Section through one of the nodules showed a brownish red and yellow cut surface. The lobules were poorly defined and irregular in shape.

**Microscopic** There was a definite thinning around many of the central veins and the lobular pattern was present, although there was not nearly as much portal fibrous tissue as one might expect. There were broad areas of scarring in some sections, and in the others the lobules showed only slight vacuolization of some of the liver cells. A few of the portal areas showed slight increase of stromal connective tissue.

**Brain** The scalp was not remarkable. The bones of the skull appeared somewhat thicker than usual and were distinctly soft. The thickness of the frontal bone was approximately 9 mm, and it was very red, suggesting marrow. The dura was not remarkable. The brain itself was distinctly porky and edematous. On the left in the region of the nucleus caudatus, there was a grayish white area of apparent gliosis and some distortion of the relationships of the nuclei to each other. The right side appeared to be entirely negative. The brain weighed 960 grams.

**Microscopic** Sections of the brain showed no striking changes except in the lenticular regions where there were occasional areas of loss of normal outline with fraying of some of the structures and with occasional foci of gliosis. Only an extremely rare large Alzheimer cell was seen. The appearance of the cortical cells showed no apparent lesion involving the third nuclear layer.

## DISCUSSION

During the six years that this patient was observed, the neurological signs showed only slow progression and the degree of cerebral dysfunction was never severe enough seriously to handicap motor function or muscular coordination. The degenerative changes affecting the liver far outstripped those affecting the lenticular nuclei, and death was directly related to the cirrhosis of the liver. Wilson has stated that the latter morbid condition rarely, if ever, gives rise to symptoms during the life of the patient, and in cases described in the literature death has been attributed to the cerebral involvement.

In this case there was a gradual development of severe portal cirrhosis with ascites, splenomegaly, and extensive esophageal varicosities. At autopsy, the liver was less than normal in size and the spleen was approximately five times normal. Esophageal hemorrhage from a ruptured varix was the immediate cause of death.

Liver function tests performed during the year before the patient's death showed severe injury. The bromsulphalein test showed a retention of 50 per cent in an hour. The total blood cholesterol was diminished, but phosphatase was slightly elevated. The Takata-Ara test was strongly positive, the pro-

thrombin time was slightly increased. There was a reversal of the albumin-globulin ratio with hyperglobulinemia. The positive Kahn reaction was explained by the hyperglobulinemia. There was slightly increased bilirubinemia. The bleeding from the gums was probably secondary to the cirrhosis of the liver, in which condition purpura is sometimes very marked. The blood showed 1-3 per cent target cells on various occasions, not an infrequent finding in patients with severe liver damage.

The present study does not cast any additional light on the etiology of this rare disease. One can only speculate as to the reasons for the progression of liver cirrhosis and the relative stationary course of the lenticular degeneration in this case. The theory which Wilson first promulgated, namely, "that the liver is first affected and that the lenticular lesions follow as the result of some unspecified toxin which either originates from, or is not neutralized by the damaged liver," seems most attractive to the writer of this paper. The lenticular nucleus, having first been affected, subsequently acquired resistance to the unspecified toxin.

### SUMMARY

A case of hepatolenticular degeneration is described, in which there was only moderate lenticular involvement in contrast to the presence of advanced portal cirrhosis, with tremendous splenomegaly. Death was caused by esophageal hemorrhage.

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## HODGKIN'S DISEASE ASSOCIATED WITH SCHILDER'S DISEASE<sup>1</sup>

By O J BATEMAN, JR, M D, GRETCHILN SQUIRLS, M D, and  
S J THANNHAUSER, M D, PH D, *Boston, Massachusetts*

THE involvement of the nervous system in Hodgkin's disease has been reported many times<sup>1, 2</sup>. Certainly, as Weil states,<sup>2</sup> it is an infrequent and late manifestation and, even then, the involvement of the spinal cord is far more frequent than that of the cerebrum.

The pathological picture of the involvement of the central nervous system by Hodgkin's disease is still unsettled. No doubts can be cast on (1) the process of direct infiltration of the central nervous system from an adjacent gland or bone, (2) infiltration of the dura itself, (3) hemorrhage secondary to the initial process, (4) infiltration of peripheral nerves. Doubtful, however, is the occurrence and etiology of destruction of nervous tissue in Hodgkin's disease as a direct result of toxemia.

The following deals with observations of a peculiar neurological involvement of a case of known Hodgkin's disease. During life this case presented a diagnostic problem as to whether the neurological involvement was a manifestation of Hodgkin's disease or a disease sui generis.

### CASE REPORT

O W B, a 43-year-old single, male needlemaker, was admitted to the Joseph H Pratt Diagnostic Hospital on October 25, 1942, because of blindness of two and a half months' duration, mental deterioration, and increasing weakness. He was referred by Dr Albert Oppenheimer of Laconia, New Hampshire.

*Present Illness.* Two years previously, he had noted a massive gland under his left arm. This was excised and the pathologist reported the presence of Hodgkin's disease. Roentgenographic treatment was given over the chest and axilla. For approximately 20 months before the onset of the present illness, he felt fairly well.

In mid-July, 1942, he noticed severe pains across the lumbar region. At onset, the pain was sharp, not accentuated by coughing or sneezing, and did not radiate down the leg. He was treated by his doctor for two weeks, after which he returned to work for three weeks. Early in August, he noted blurring of vision, and because of this, his glasses were changed. After driving to Boston from Laconia to see a ball game, he described the players on the field as slightly blurred and he sometimes saw two where there was one. His vision became worse and bifocal glasses were prescribed, but there was no improvement. He was admitted to the Boston City Hospital September 3, and a diagnosis of diffuse Hodgkin's disease with meningeal involvement was made. Roentgenographic treatment to the skull was advised, and despite nausea and vomiting, he received approximately two treatments a week for three weeks with no improvement.

He stated assuredly, as did his mother, that the entire process had been slow and insidious. No injections or medications had been given which might produce blindness.

Past history was very sketchy. The patient did not talk with any coherency and the information obtained from his mother was non-contributory. His past health had

\* Received for publication July 19, 1943.

From the Joseph H Pratt Diagnostic Hospital and Tufts College Medical School.

been good. An appendectomy had been performed 15 to 20 years before. There had been no injuries, serious disease, diplopia, scotomata, or headaches. There was no history of any familial neurological disease or lymphadenitis, and venereal disease was denied.

*Physical Examination* The patient was blind and confused. He could recognize no objects or forms in front of him, nor could he answer questions rationally. Temperature 100° F, pulse 115, respirations 18. Height 5 feet, 6 inches, weight 124 pounds. Results of the examination of the corneae, conjunctivae, and sclerae were negative (see neurological examination below). The uvula deviated slightly to the left and the tongue showed no papillary atrophy or evidence of glossitis. There was no salivary drooling. The neck showed no glandular or thyroid enlargement. The chest was clear to auscultation and percussion. The heart rate was rapid and the rhythm regular. There was a slight, soft, blowing systolic murmur over the apex.  $A_2$  was greater than  $P_2$ . The spleen was palpable only on deep inspiration, but the liver and kidneys were not felt. No tenderness, masses, ascites, or herniae were noted. On neurological examination, he responded slowly to questions and was slightly disoriented. His speech was very dysarthric and he did not follow commands. The pupils did not react to light. The eye movements could not be tested. The left disc appeared atrophic, whereas the right was fairly normal. The facial movements were good. The palate moved to the left, and the tongue could not be protruded. Spontaneous movements of all extremities were possible. The right arm appeared weak. The deep reflexes were depressed in the arms. Knee kicks were present, but the ankle jerks were not obtained in bed. Babinski reflex was obtained on the right foot, whereas the left was normal. He felt pain in both sides. Stereognosis could not be tested.

*Laboratory Examination* The results of the urine examination were negative. Blood hemoglobin 69 per cent (Sahli), red cell count 4,040,000, white cell count 7300, the differential count was normal. Spinal and blood serological examinations were negative. Blood sedimentation rate (Westergren method) was 103 mm in one hour. Lumbar puncture pressure 275 mm, rise and fall, slow and jerky, jugular pressure bilaterally, 400 mm, good rise on deep inspiration and coughing, fluid clear, final pressure, 200 mm, partial block. The cell count showed no red cells, lymphocytes numbered 45 per cu mm with Unna's methylene blue. No increase in protein was found in Pandy's test. The protein content of the spinal fluid was 22 mg per cent. The results of a gold-sol test were negative, as were the Hinton and Wassermann tests.

*Röntgenographic examination* of the skull showed no evidence of any abnormality. The mediastinal glands in the chest, particularly on the left side above the aortic notch, were enlarged.

The patient's mental deterioration progressed rapidly while he was in the hospital. Death occurred five days after his hospital discharge, and was preceded for 24 hours by total paralysis.

*Anatomic Diagnosis* A Lymphoblastoma (probably Hodgkin's) with 1 Involvement of lymph nodes of posterior mediastinum, periaortic, peri-iliac and inguinal regions, of hilus of lung, liver and spleen, compression of common duct by lymph nodes with distention of gall-bladder and icterus of skin and sclera. Compression of abdominal aorta, vena cava inferior and left iliac artery and veins. 2 Metastases to liver and spleen.

B Bilateral atrophy of gray matter of occipital lobes. Bilateral degeneration and softening of white matter of both occipital lobes extending as far into the substance of the brain as the posterior portions of the walls of the lateral ventricles. Swelling and softening of internal capsule and basal ganglia particularly in the so-called post-limbic. Question of very slight softening in subcortical white matter in

the region of the left parietal lobe, capillary hemorrhage into the posterior lateral wall of posterior horn of left lateral ventricle

C Atrophy of medial portion of caudate nucleus (bilaterally) adjacent to foramen of Munro Abnormally large third ventricle

D Bilateral cysts of choroid plexus

E Degeneration and atrophy of white matter of pons and of white matter and olivary body of medulla

F Arteriosclerosis, generalized

G Pigmentation (brownish) of both lower extremities, flabby musculature of heart

H Congestion of lungs, liver, spleen and kidneys

I Postoperative fibrous adhesions between cecum (site of appendectomy) and parietal peritoneum, fibrous adhesions between spleen and diaphragm

*Microscopic Examination* There was widespread demyelination, most marked in the areas noted in the gross. In some areas there was a striking gliosis. In other areas edema and gutter cells dominated the field. Changes involving nerve cells were numerous and apparently depended upon or were secondary to changes affecting the myelin. There were no lymphogranulomatous tumor nodules in the substance of the brain.

The Hodgkin's lesions noted in the gross were typical of lymphogranuloma of the Hodgkin's type.

## DISCUSSION

This case was observed constantly after the diagnosis of Hodgkin's disease had been established by biopsy of a gland and treated with 3840 skin doses of roentgen-ray. On examination at the Pratt Diagnostic Hospital, he showed no visible sign of Hodgkin's disease except a mediastinal mass demonstrable by roentgen-ray only. The result of roentgenographic treatment seemed almost perfect, as regarded visible manifestations of the disease. However, two years after the diagnosis of the disease was established (by biopsy of the gland), the involvement of the nervous system suddenly presented itself. The signs and symptoms were double vision, impairment of vision, followed shortly by bilateral occipital blindness, speech difficulty, agnosia, asynergia, and progressive mental deterioration. The possibilities that confronted us in diagnosis were (1) involvement of the brain by Hodgkin's disease, (2) a diffuse process involving the parenchyma of the brain by inflammation, encephalitis disseminata, (3) a degenerative disease as described by Schilder et al (encephalitis periaxialis diffusa).

In answer to the first question, we did not feel justified in making a diagnosis of Hodgkin's disease involving the meninges and brain parenchyma because of the symptoms of the patient, namely, double vision, blindness, mental deterioration, agnosia, and asynergia. Lymphomatous involvement of such extensiveness seemingly should be due to large meningeal masses penetrating the brain substances. Such masses should result in pressure symptoms and should manifest themselves by increased spinal fluid proteins, pleocytosis. The fluid of this case as shown above had slightly elevated pressure (275 mm of water, proteins 22 mg, and only 45 lymphocytes), a finding hardly consistent with such brain involvement caused by meningeal masses. The most impressive finding in this case was a bilateral occipital-temporal-parietal-cortical syndrome resulting in blindness and mental deterioration. We must admit that some of our

neurological consultants thought that such history and findings could be consistent with extension of a lymphomatous process

In the second possibility, acute disseminated encephalitis, the course is generally fulminating in nature and the meningeal signs and spinal fluid findings of increased cells and protein are absent in this case. However, the clinical picture<sup>2</sup> of acute disseminated encephalitis is so diverse that only the outcome (a

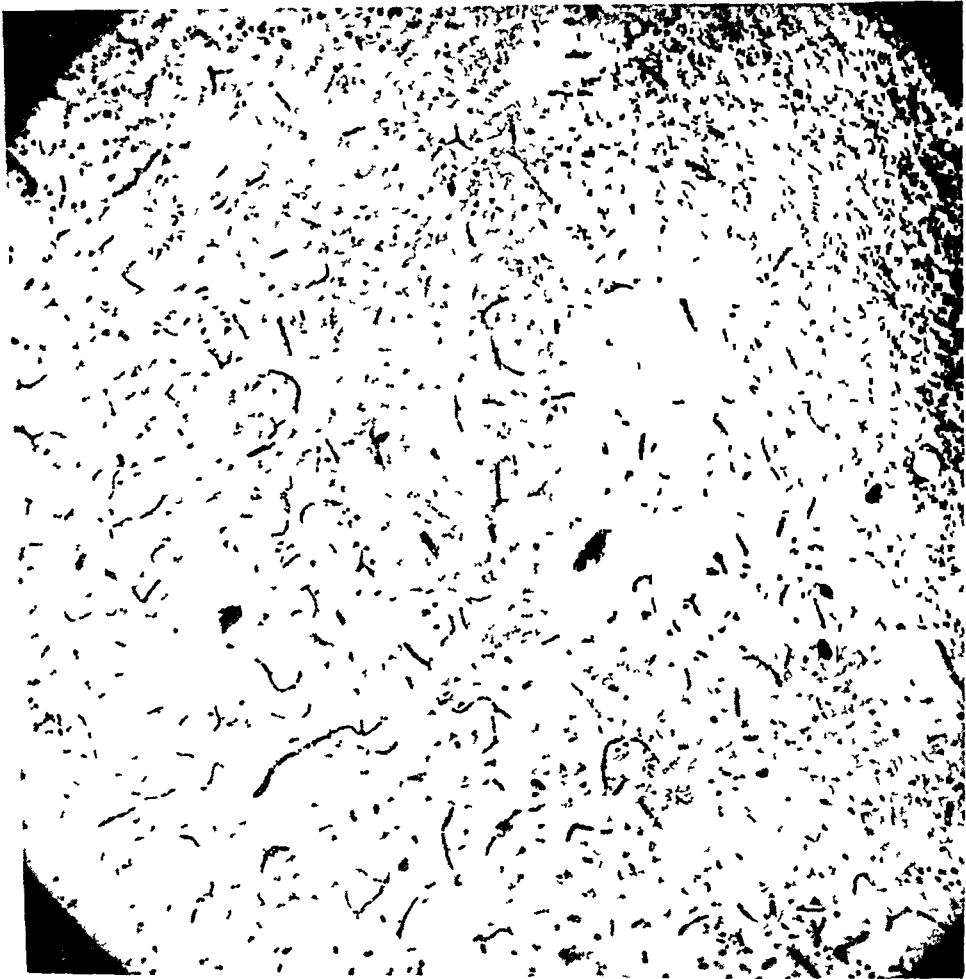


FIG 1 Low power photomicrograph of occipital area of cerebrum showing areas of demyelination

fatal issue is infrequent) and the pathological findings could definitely eliminate this possibility entirely

Acute disseminated encephalitis was described in Hodgkin's disease by Allen et al and by Weil<sup>1</sup> (three cases). In one case of Weil's staphylococci and streptococci were found in the metastatic brain lesions, the second case showed a large retropharyngeal abscess which resulted in hemorrhagic foci in the brain and spinal cord, and the third case showed hemorrhagic foci with perivascular foci of inflammation

There was no focus in our case which may have resulted in an encephalomyelitis. We believed, however, that the clinical picture in the above case was

that of the degenerative disease described by Schilder et al because the symptoms of the patient fitted the end stages of Schilder's disease so perfectly described by Wilson<sup>1</sup> "Blind, paralyzed, incontinent Death is a happy end"

The reported pathological findings were uniformly consistent with our diagnosis in that the underlying disease of the brain was not an extension of Hodgkin's disease or encephalitis disseminata, but a diffuse demyelination process with bilateral symmetrical involvement. It is not our purpose to discuss here the different clinical syndromes which start with demyelination and end with diffuse sclerosis of the central nervous system as Schilder's disease. We wish only to demonstrate by this case that a very outspoken condition of demyelination may co-exist with Hodgkin's disease without signs of that disease in the meninges or brain or scarring resulting from previous implantations destroyed by roentgen-ray as described by Weil<sup>1</sup>

Once again we inadvertently raise the question of the pathogenesis of Schilder's disease. Is the etiology an abiotrophic inherent degenerative process, or as in our case a demyelination that may have resulted from the injurious effects of roentgen-ray therapy or a degeneration resulting from a concurrent infection or neoplastic disease?

If we accept the abiotrophic degeneration process, we must believe two diseases coexisted in the above reported case (i.e., Hodgkin's disease and periaxialis diffusa—Schilder's disease). This possibility is difficult to conceive because the degenerative type of periaxialis diffusa does not progress as rapidly as the above case and generally shows a familial incidence (Wilson)<sup>3</sup>

As regards the demyelination as a result of roentgen-ray therapy, the pathologic lesions of the above case did not show the manifestations of brain injury by roentgen-ray, reported by various authors,<sup>4, 5</sup> namely numerous extensive foci of necrosis of tissue, fibrosis of the vessels, and deposition of peculiar homogenous substances in the wall of the vessel, consisting of impregnation of the elastic layer with dust-like fatty material and the development of foam cells in the intima and lumen similar to hyalinization known sometimes as "Alzheimer's colloid degeneration"

It would be difficult to conceive, in the face of the above description of roentgen-ray damage of the brain, that roentgen-ray injury could produce a picture of Schilder's disease. Our search of the literature revealed no such report.

There remains only the possibility that a peculiar process caused by Hodgkin's disease did produce the pathological picture of encephalitis periaxialis diffusa (Schilder's disease) in our case. Such a possibility of a toxin from a distant source damaging brain parenchyma has been postulated by Shapiro,<sup>6</sup> but doubted by Weil<sup>1</sup> and Conybeare.<sup>7</sup> The cases of Shapiro did not show the demyelination in the cerebrum which our case exhibited. We cannot offer our case as proof of the fact that lymphogranulomatous tissue of the Hodgkin's type can release a noxious agent (toxin?) which may act upon brain tissue in such a way that demyelination results, but we can only say that the case described offers evidence that this may be a possibility.

#### SUMMARY

In a case of Hodgkin's disease of two years' duration, there occurred the clinical and histological picture of encephalitis periaxialis diffusa (Schilder's disease)

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PRIMARY MYCOTIC ANEURYSMS<sup>1</sup>

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THE extreme rarity of case reports of primary mycotic aneurysms and their potential hazard as foci of subsequent infection prompted the author to review the literature, summarize the cases to date, and report one of his own. In addition, it is desired to call attention to the fact that primary mycotic aneurysms, if accessible to surgical approach, may be completely eradicated. Thus, from the standpoint of prognosis they are similar to traumatic aneurysms rather than the far more grave mycotic aneurysms secondary to bacterial endocarditis.

The adjective "mycotic" appears to have been coined by Osler<sup>2</sup> to signify those aneurysms of infectious origin, resulting from the presence and multiplication of bacteria within the lesion. In subsequent years a special group of diseases has been called mycoses, but the long usage of mycotic, in the above sense, has resulted in its firm establishment in medical literature. The term "primary mycotic aneurysm" was defined by Crane<sup>35</sup> as "a lesion developing in the wall of an artery which is not associated with any demonstrable intravascular inflammatory focus, as bacterial endocarditis, or with any in the surrounding tissue." In the opinion of the author the phrase primary mycotic aneurysm is synonymous with mycotic aneurysm of extravascular origin, provided the focus is not immediately adjacent to the artery.

Twenty-three cases have been found which appear to have been primary mycotic aneurysms (chart 1). In 13 of these cases the authors<sup>8, 10, 13, 14, 16, 20, 22, 23, 27, 29, 34, 35, 36</sup> were able to recognize the primary focus and to demonstrate the etiological agent. In five instances the authors<sup>17, 18, 26, 30, 33</sup> were able to show the primary focus, but not the etiological agent. In one instance Oliver<sup>3</sup> demonstrated bacteria in the lesion but failed to give the primary focus. Holst<sup>6</sup> found gram positive diplococci and cocci in chains in the aneurysmal lesion but

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This work was completed before the author entered the Military Service



CHART I

Author	Year	Age	Sex	Primary Focus	Associated Intravascular Lesions	Site of Mycotic Aneurysm	Etiology
Ruge <sup>8</sup>	1905	12	M	Cellulitis left foot Osteomyelitis left femur	None	Left coronary artery	Staphylococcus and streptococcus
Vanzetti <sup>10</sup>	1907	68	—	Bronchopneumonia	None	Ascending and thoracic aortas Superior mesenteric artery	Diplococcus of Frankel
Scheuer <sup>13</sup>	1910	—	M	Phlegmon of leg	None	Ascending aorta	Diplococcus
Köster <sup>14</sup>	1910	17	M	Gonorrheal urethritis	None	Ascending aorta	Gram negative diplococcus
Koritschoner <sup>15</sup>	1912	30	M	Phlegmon right hand	None	Subclavian artery	Streptococcus
Thayer <sup>20</sup>	1922	28	M	Gonorrheal (?) arthritis Right ankle and shoulder	Old healed endocarditis	Ascending aorta	Gram negative diplococcus Gram positive coccus
Lindau <sup>22</sup>	1924	38	F	Acute gonorrhea with salpingitis	Old healed endocarditis	Ascending aorta	Gonococcus
Reifenstein <sup>3</sup>	1924	10½	M	Epidemic nasopharyngitis	Congenital anomaly descending aorta	Descending aorta	Pneumococcus
Feller <sup>27</sup>	1930	27	M	Throat infection	None	Celiac artery	Gram positive diplococcus and cocci in chains
Aschner <sup>29</sup>	1932	23	F	Gonorrheal arthritis	Old healed endocarditis	Ascending aorta	Biscuit shaped diplococcus
Preioni et al <sup>34</sup>	1936	48	M	Ill defined pulmonary disease	Perianeurysmal pneumococcal abscess	Abdominal aorta	Pneumococcus
Crane <sup>35</sup>	1937	35	M	Cellulitis right foot	Hypoplasia of aorta Old healed endocarditis	Arch of aorta Superior mesenteric artery	Gram positive coccus
Campana <sup>36</sup>	1939	32	M	Cellulitis right knee	None	Abdominal aorta	Staphylococcus
Oliver <sup>3</sup>	1891	36	M	—	None	Ascending aorta	Anthrax morphologically
Holst <sup>6</sup>	1901	25	M	Gonorrhea (?)	None	Arch of aorta	Gram positive diplococcus and cocci in chains
Witte <sup>9</sup>	1905	—	—	Staphylococcal pyemia?	None	Arch of aorta	—
Endenhuizen <sup>17</sup>	1914	60	—	Phlegmon right hand	None	Arch of aorta	—
Merkle <sup>18</sup>	1920	—	—	Cystitis	None	Ascending aorta Bifurcation of abdominal aorta	—
Clerc and Bascourret <sup>6</sup>	1929	24	M	Arthritis left elbow and right ankle	Old healed endocarditis	Ascending aorta Left subclavian artery	—
Garland <sup>30</sup>	1932	—	—	Pneumococcal septicemia?	None	—	—
Virgilio <sup>33</sup>	1935	30	—	Streptococcal septicemia?	None	Arch of aorta	—
Eichelster and Knoflach <sup>24</sup>	1926	—	—	—	Old healed endocarditis	Right gastroepiploic artery	None found
Clutton and Dudgeon <sup>11</sup>	1908	78	M	Lobar pneumonia	—	Left femoral artery	Pneumococcus

attributed the primary focus to acute gonorrhea, this probably represented a streptococcal infection secondary to the primary gonorrheal urethritis and arthritis. Witte<sup>9</sup> demonstrated only that the aneurysm in his case was due to an infectious process not associated with endocarditis and was not clear whether the aneurysm resulted from bacterial growth in the vasa vasorum or from erosion from the left main bronchus. Eichelter and Knoeflach<sup>24</sup> reported a case with the histopathological appearance of a mycotic aneurysm but were unable to culture an organism or to find any bacteria in the sections. The final case that has been accepted was the clinical report by Clutton and Dudgeon<sup>11</sup> of a case of aneurysm developing in the left femoral artery three months after a right upper lobar pneumonia. The artery was ligated, but the wound became suppurative and pneumococci were cultured from the exudate. The patient recovered and the authors were unable to find any abnormality in the cardiovascular system which would serve as the primary focus.

In addition to the 23 cases that have been accepted as primary mycotic aneurysm there are 11 additional reports in the literature that deserve brief comment. Quincke<sup>1</sup> reported a case of aneurysm of the hepatic artery which he ascribed to typhoid fever but offered no proof that it was mycotic. Gils<sup>4</sup> and Hecker<sup>5</sup> reported cases with aneurysm of the aorta which they attributed to typhoid fever but offered neither proof of the typhoid fever nor proof that the aneurysms were mycotic. In Jordan's case<sup>7</sup> there was an aneurysm of the ascending aorta following otitis media which he considered to be the result of emboli in the vasa vasorum, but this lesion showed no evidence of bacterial infection. Cathcart<sup>12</sup> considered the aneurysm of the femoral artery to have been the result of typhoid fever but offered no proof. His case recovered after operation. In the case reported by Moriani<sup>15</sup> the aneurysm was thought to be embolic but the necropsy protocol was not given. The clinical report by Jonsen<sup>19</sup> of mycotic aneurysm of the hepatic artery following influenza was without proof. The mycotic aneurysm reported by Gioja<sup>25</sup> was adjacent to a suppurative process in the lung and was considered to be an aneurysm "per arrosioneum". In the case reported by Lambert and Secretan<sup>28</sup> the aneurysm of the hepatic artery followed pneumonia but they gave no other description of the lesion. Hansmann and Schenken<sup>31</sup> reported a case of aneurysm of the basilar artery associated with melitensis meningo-encephalitis which they called mycotic due to *Brucella melitensis* var. suis. The authors gave no proof that it was mycotic and not congenital. In Taylor and Reinhart's case<sup>37</sup> the aneurysm of the right common iliac artery was considered to be secondary to the periureteritis produced by the indwelling catheter. The case reported by Lippincott<sup>38</sup> of dissecting aneurysm of the abdominal aorta with suppuration had shown a positive culture of streptococci from the blood before death. From the description of the lesion it seems likely that the suppuration took place secondary to the old dissecting aneurysm.

#### CASE REPORT

A 60 year old unconscious white man was admitted to the University Hospital on June 16, 1940. It was learned that the patient had been in good health until February of that year when he developed lobar pneumonia of the left lower lobe and was admitted to another hospital in an unconscious state. His pneumonia was due to the

pneumococcus type VII. He was treated with oxygen and sulfapyridine for five days when chemotherapy was discontinued because of a rash. His recovery was slow but uneventful. Approximately two weeks after the patient returned home, he had a return of his cough and weakness. During the next four months he suffered frequent attacks characterized by chills and fever, but in the intervals between attacks, he was able to be out of bed although he was very weak. Four days prior to his final admission he had a severe chill followed by a fever of 103° F. Again the night before admission he suffered another severe chill and became unconscious, remaining in that state until admission.

As far as could be ascertained from his family, the past history and systems review contributed no other pertinent data.

Physical examination at the time of admission revealed a slender, elderly white male in an unconscious state. Rectal temperature was 104.6° F, pulse rate 148 per minute, and respirations were 32 per minute. The skin was hot and dry and without lesions. The pupillary reflexes were present and active, the fundus oculi were within normal limits for his age. The mouth and pharynx were covered by desiccated mucus. The heart was within normal limits as to size by percussion, the rhythm was regular, no murmurs were heard, and the blood pressure was 130 mm Hg systolic and 70 mm diastolic. The lung fields were resonant to percussion, the breath sounds were vesicular and there was slight suppression, with rhonchi at both bases. Palpation of the abdomen was without note except that the urinary bladder was four fingers' breadth above the symphysis pubis. Rectal examination revealed that the prostate was slightly enlarged, but was of normal consistency. The neurological examination showed marked cervical rigidity, hypoactive deep reflexes, and a positive Babinski's sign on the left. The patient failed to respond to painful stimuli.

Laboratory findings were: Hemoglobin 92 per cent (Sahli), red blood cells 4.7 million, white blood cells 21,000, polymorphonuclear leukocytes 94 per cent, lymphocytes 4 per cent, mononuclear leukocytes 1 per cent, myelocytes 1 per cent. Urinalysis: acid in reaction, albumin absent, sugar 3 plus (following intravenous dextrose), acetone absent, and microscopic examination negative. A serological test for syphilis was negative. Blood non-protein nitrogen was 33 mg per 100 c.c., blood sugar 286 mg per 100 c.c. (following intravenous dextrose), carbon dioxide combining power 45 volumes per cent. Spinal fluid: 320 millimeters of water pressure, cloudy, 4100 leukocytes per cubic millimeter, 100 per cent polymorphonuclear leukocytes, many gram positive diplococci which on culture and typing proved to be pneumococcus type VII, globulin was 4 plus. There was no record of a blood culture.

Despite repeated attempts to find the focus for the pneumococcic meningitis, none was found. The sinuses, ears, and pharynx revealed no abnormalities. An endocarditis was suspected but various examiners failed to find any clinical evidence of cardiac involvement.

The patient was given sodium sulfapyridine intravenously and a total of 365,000 units of type VII antipneumococcus serum together with intravenous dextrose and normal saline. Consciousness was never regained, and he died on June 19, 1940, three days after admission to the hospital.

The necropsy was performed by Dr. C. G. Warner approximately four hours after death. The anatomical lesions of note were confined to the brain and the cardiovascular system.

The brain weighed 1250 grams. The hemispheres were symmetrical. There was a gray purulent exudate covering both hemispheres and associated with moderate injection of the superficial vessels. There was considerable purulent exudate in the leptomeninges over the base and especially in the region of the cisterna magna. The basilar arteries showed a moderate sclerotic change. Both lateral ventricles were slightly and symmetrically dilated and contained purulent exudate on the ependymal

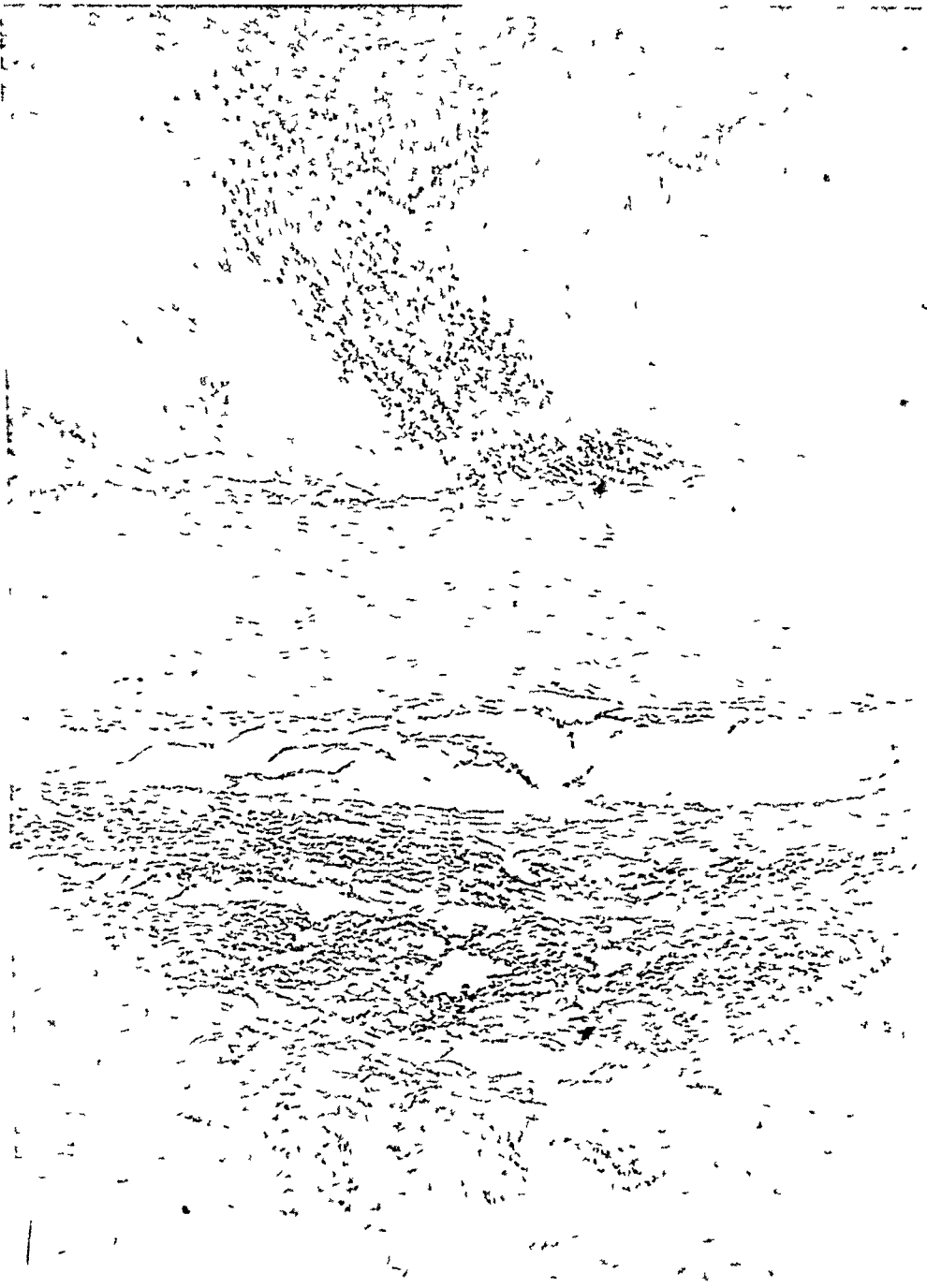


FIG 1 Section of aneurysmal wall showing leukocytic infiltration in adventitia, relatively normal media and a portion of the attached thrombus



FIG 2 An adjacent section of the aneurysmal wall showing infiltration of the media by acute inflammatory cells

surfaces. There was a massive collection of pus about the optic chiasm which extended laterally into both Sylvian fissures. The third ventricle was filled with pus.

The heart weighed 385 grams. The epicardial surface was roughened and glazed with both fine and coarse fibrin and a few petechiae. There were postmortem clots in all the chambers of the heart. There were no vegetations on any of the valves. The valvular measurements were aortic 7.5 centimeters, mitral 10 centimeters, tricuspid 12.5 centimeters, and the pulmonic 8 centimeters. The aorta presented two saccular aneurysmal dilatations a few centimeters above the aortic ring, each of which measured 2.5 centimeters in diameter and was filled with laminated thrombi. There was an abrupt margin between the normal aorta and the aneurysms. At the bifurcation of the abdominal aorta there was another aneurysm measuring 3 centimeters in diameter which was filled to the level of the surrounding aorta with a thrombus which extended into the right iliac artery.

Microscopic sections through the aneurysmal wall showed liquefaction and destruction of the medial substance with areas of scar and granulation tissue. The inner surface was coated with a thick organizing thrombus that contained focal patches of leukocytes. Special bacterial stains (MacCallum's) revealed gram positive diplococci.

The anatomical diagnosis was Saccular aneurysms, aorta, multiple, mycotic, root of the aorta and bifurcation, leptomeningitis, purulent, diffuse, acute fibrinous pericarditis, cloudy swelling of viscera, pulmonary congestion and edema, pleural adhesions, left, anomalous lobulation of lung, right (four lobes).

### DISCUSSION

In attempting to reconstruct the sequence of events in this case certain facts are paramount: a type VII pneumococcic lobar pneumonia, four months of recurrent attacks of chills and fever, and a terminal type VII pneumococcic meningitis.

The absence of knowledge of an associated bacteremia in the original infection makes it impossible to trace positively the chronological order of events. However, the known facts lead one to the conclusion that the original lobar pneumonia gave rise to a mycotic aneurysm which became the focus for the terminal meningitis. It is hardly possible to explain the findings in the case without assuming that a bacteremia did exist.

In 1923, Stengel and Wolferth<sup>21</sup> made an extensive review of the literature on mycotic aneurysms and were able to collect only 217 cases, of these, 187 showed definite evidence of endocardial origin. The remainder were rheumatic, aneurysms by erosion and primary mycotic. They concluded that mycotic aneurysms of intravascular origin may arise in any one of three ways: (1) by lodgment of infected emboli in the lumen of vessels or in the vasa vasorum, (2) by the settling of bacteria on the intima of a vessel or in the vasa vasorum, and (3) by continuity or contiguity of infection from the aortic or pulmonic valves. As the scope of this paper is concerned with mycotic aneurysms of extravascular origin, there remains only the possibility of the settling of bacteria on the inner surface of a vessel or in the vasa vasorum. Unfortunately, which of the two methods was responsible does not readily admit of definite proof. One may easily theorize from the anatomical arrangement of the blood supply to the aorta that the most probable mode of infection was through the vasa vasorum, for the volume and velocity of blood flow in the aorta would not favor the lodgment and development of bacteria on an undamaged intima.

From the above facts and theory it seems that the following was the chronological order of events a type VII pneumococcic lobar pneumonia of the left lower lobe, an associated bacteremia resulting in the lodgment of pneumococci in the vasa vasorum of the ascending aorta and at the bifurcation of the abdominal aorta, then subsequent multiplication resulting in three mycotic aneurysms, the periodic release of pneumococci into the blood stream from these foci, giving rise to the periodic episodes of sepsis and finally to the terminal type VII pneumococcic meningitis

### COMMENT

The above case brings the total to 24 primary mycotic aneurysms in the medical literature. In the 17 cases in which the causes were given, four showed two bacterial agents either culturally or morphologically. In six instances the pneumococcus was found, in six the streptococcus, in four the gonococcus, and in two the staphylococcus. In one case an organism morphologically indistinguishable from the bacillus of anthrax was demonstrated, and in one lesion resulting from a phlegmon of the leg diplococci were observed. In the final case, presumably resulting from gonorrhea gram positive diplococci were seen.

Of the 19 cases in which the age was stated, 58 per cent occurred in the third and fourth decades of life. Of the cases in which the sex was noted 82 per cent occurred in males. The primary focus varied widely and apparently was inconsequential per se. Although 69.5 per cent of the necropsies showed no associated intravascular lesions, 26 per cent were associated with a healed endocarditis and 8.7 per cent occurred in association with a congenital abnormality of the aorta.

In five cases there were two or more mycotic aneurysms. The ascending aorta was involved 10 times, the aortic arch, five times, the abdominal aorta, four times, the descending thoracic aorta, twice, the superior mesenteric artery, twice, the subclavian artery, twice, and the celiac, right gastroepiploic, and left femoral arteries once each.

In two, or 8 per cent of the 24 cases the mycotic aneurysm was accessible to surgical approach, namely in the cases involving the left femoral artery and the right gastroepiploic. In the case of the femoral artery it was recognized and eradicated by surgical intervention.<sup>11</sup> In Cathcart's case,<sup>12</sup> although not a proved primary mycotic aneurysm, the lesion of the femoral artery was successfully removed surgically. In 1934, Gage<sup>3</sup> successfully operated on a mycotic aneurysm of the right common iliac artery which he considered secondary to a healed bacterial endocarditis.

Primary mycotic aneurysms present no distinctive symptomatology but, as in the case of all other saccular aneurysms, produce their symptoms by size and position. In addition to the symptoms that they have in common with all saccular aneurysms, primary mycotic aneurysms also are associated with some degree of sepsis. This is most frequently manifested by periodic febrile episodes, often accompanied by chills and usually with moderate leukocytosis.

Although it is impossible to give a definite symptom complex for primary mycotic aneurysms, it is the opinion of the author that the possibility of their presence should be suspected (1) whenever an aneurysm during its process of development presents evidence of infection, (2) when an acute infectious dis-

case is probably the result of a bacteremia from an obscure focus, especially if this was antedated by an illness due to the same bacterial agent. It seems justifiable to consider a mycotic aneurysm as primary if there is no evidence of an endocarditis nor a suppurative process adjacent to the lesion.

### SUMMARY

1 The existence of primary mycotic aneurysm as a clinical entity is emphasized and the literature on this subject reviewed and summarized.

2 The importance of early diagnosis and surgical removal, if possible, of primary mycotic aneurysms is stressed.

3 A case report of a primary mycotic aneurysm following a type VII pneumococcal pneumonia is presented.

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## ACUTE CORONARY ARTERY OCCLUSION WITH INTRA- VENTRICULAR SEPTAL PERFORATION, BERNHEIM SYNDROME, AND SUPERIOR VENA CAVA OB- STRUCTION, DIAGNOSED CLINICALLY\*

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### CASE REPORT

THE patient, age 47, Captain USN, was admitted 4 a m June 15, 1942, two hours after an attack of severe precordial pain The Captain had been in the regular Navy

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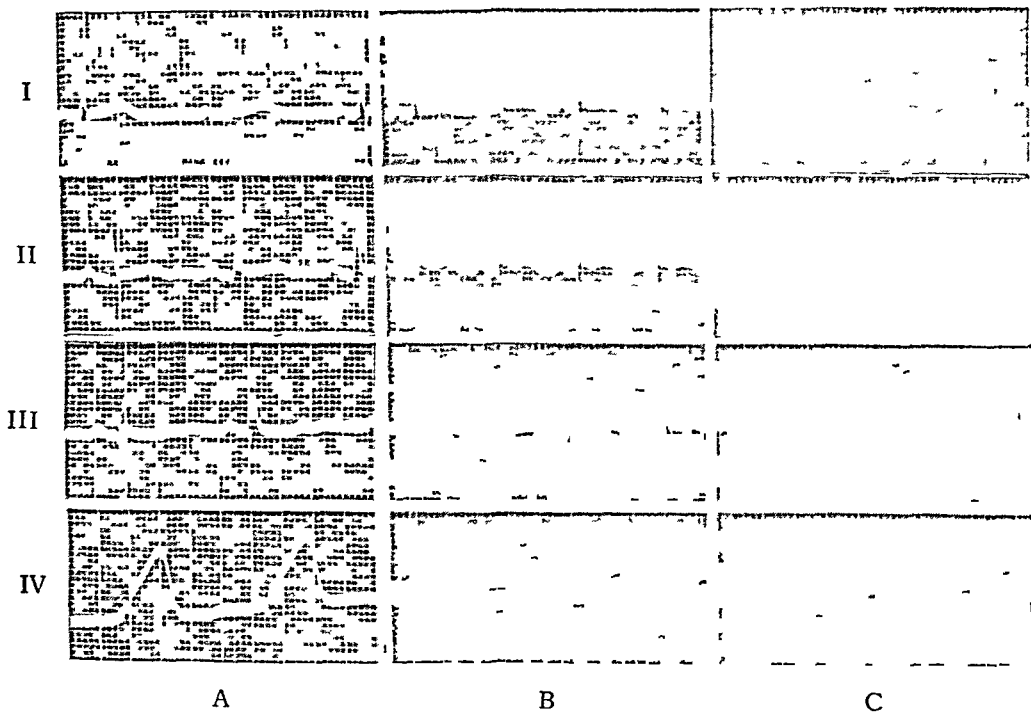
over 25 years. He had had no major illnesses. His blood pressure had been about 140 mm Hg systolic and 80 mm diastolic. Close questioning revealed that two years previously the patient had experienced a severe upper epigastric pain relieved by bicarbonate of soda and that two months prior to admission he had many mild similar experiences. It should be noted that this naval officer had performed strenuous duty for some time before and had worked particularly hard a few months preceding the present illness. By this is meant long hours, considerable traveling and irregular habits. The morning in question, he had been awakened by epigastric distress which soon developed into a severe crushing precordial pain with radiation down both arms, the pain in the left side being more severe. A physician was called and found the patient in "semi-shock" and he administered  $\frac{1}{2}$  grain of morphine sulphate by hypodermic injection.

Physical examination disclosed a well-developed and well-nourished man. His muscles were excellently developed. The patient was perspiring freely with a

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P. L. M., m, 47, Capt USN. Died June 26, 1942 after 11 days illness. Coronary occlusion, anterior and posterior infarction, diffuse pericarditis, ruptured interventricular septum, Bernheim syndrome.

FIG 1-A, June 15, 1942. Reveals a regular sinus rhythm with a rate of about 66 per minute. There are elevations of the RS-T segments in all leads except the third. The elevation in the chest, or precordial lead is marked and immediately suggests acute coronary artery occlusion involving the anterior wall of the left ventricle. (Also the small polyphasic m-shaped QRS in this lead is seen in acute anterior wall infarction due to coronary occlusion.) The Q-waves in Leads II and III indicate posterior wall infarction. The reciprocal relationship between Leads I and III are clearly shown, namely, elevated RS-T, depressed T<sub>1</sub>, upright T<sub>1</sub>, inverted T<sub>3</sub>.

FIG 1-B, June 17, 1942. The elevations are present in all leads suggesting pericarditis.

FIG 1-C, June 20, 1942. Q<sub>1</sub> has become definite, confirming anterior wall infarction and Q<sub>2</sub> and Q<sub>3</sub> have become larger, confirming posterior wall infarction. The RS-T elevation in the chest lead has progressed to inverted T-waves, a classical change in coronary occlusion.

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P L M, m, 47, Capt USN Continued

FIG 1-D, June 22, 1942 Now there is auricular flutter with an auricular rate of about 290 and a ventricular rate of one-half that. Right axis deviation has appeared, a not uncommon occurrence in coronary occlusion.

FIG 1-E, June 23, 1942 A simple tachycardia is present.

FIG 1-F, June 25, 1942  $T_3$  is now definitely inverted.

temperature of 97.0° F by mouth, pulse 88, respirations 20, and blood pressure 105 mm Hg systolic and 80 mm diastolic. The heart sounds were tic-tac in quality and distant. There were no murmurs, accentuations, or irregularities. The lungs were clear. The liver was not enlarged.

The initial electrocardiogram taken six hours after the onset of his pain revealed a regular sinus rhythm, rate 66 per minute, with Q waves in Leads II and III, inversion of  $T_3$ , and elevation of RST segment in Leads I, II, and IV. The electrocardiographic diagnosis was acute coronary occlusion.

The sedimentation rate, Kahn test, and urine examination were normal. On the second day of hospitalization a leukocytosis of 14,800 was present.

The pain persisted in spite of large doses of opiates, and it was necessary to use an oxygen tent with 50 per cent oxygen concentration. Nausea and vomiting were present. Because the patient was unable to void, he had to be catheterized twice daily.

No pericardial rub was heard, but a gallop rhythm appeared on the second day, and suddenly on the evening of the third day a thrill was felt and a loud apical systolic murmur was heard for the first time to the left of the sternum at the level of about the fourth intercostal space. Diagnosis was promptly made of interventricular septal perforation. The blood pressure was down to 90 mm Hg systolic and 70 mm diastolic. The heart rate rose to about 100 and the temperature to 101.0° F by mouth on the fourth day. At this time there was a complete disappearance of the left radial pulse, and no blood pressure reading could be obtained in this arm. This extremity

was colder than the right. It was suspected that an embolism had occurred in the left brachial or left radial artery. The electrocardiogram showed progressive changes. The RS-T waves became elevated in all leads and the  $Q_4$  appeared. The elevation of the RS-T in all leads was interpreted as indicating a massive infarction involving both the anterior and posterior surfaces of the left ventricle ( $Q_2$  and  $Q_3$  for the posterior wall and  $Q_4$  for the anterior). On the seventh day the temperature rose to 102.0° F by mouth and remained that high thereafter. The patient began to lose ground rapidly and became semi-delirious. On the eighth day his pulse was irregular and rapid and the electrocardiogram revealed the presence of an auricular flutter, with an auricular rate of 290 and a ventricular rate of 145, i.e., a 2-to-1 flutter. Following a test dose of quinidine, he was given 1 gram of this drug within the next 18 hours, and the rhythm returned to normal. Right axis deviation finally appeared on the electrocardiogram.

On the tenth day, the patient became rather cyanotic and the jugular veins distended and since there was no marked congestion of the lungs a diagnosis of Bernheim syndrome was made, i.e., a bulging or herniation of the septum into the right ventricle. The septal perforation in a way confirmed this as it indicated that the septal wall was weak and left intraventricular pressure forced the wall into the right cavity. This further caused obstruction with increased venous pressure in the jugular veins. There was no dependent edema. The liver edge was only just palpable, and moist râles appeared at the lung bases.

Because the cyanosis became limited to a horizontal line on the upper chest at the level of the second intercostal space, a diagnosis of superior vena cava thrombosis was made. The presence of heart failure with the undoubted slowing of the blood stream, the probable presence of mural thrombi in the ventricular walls were elements that also suggested this condition.

The patient became uncomfortable lying flat. A period of Cheyne-Stokes respirations lasted for about two days.

On the tenth day, the non-protein nitrogen of the blood was found to be 187.5 mg per 100 c.c. and the urea nitrogen 140 mg per 100 c.c. No red blood cells were found in the urine. The azotemia was thought to be due in part to heart failure and partly to the shock and drop in blood pressure and partly to dehydration (the patient had perspired profusely all the time in spite of the fact that he was not taking more than 1000 c.c. of fluid daily). In the evening of the tenth day, the patient lapsed into fairly deep coma and died on the eleventh day.

## DISCUSSION

The clinical diagnoses were as follows:

- 1 *Coronary artery occlusion* because of the severe pain, shock, fever, leukocytosis, drop in blood pressure, diminished intensity of heart sounds with gallop rhythm, and a specific electrocardiogram—elevations of the RS-T segment with progressive inversions of the T-waves, large Q-waves, and a reciprocal relationship of the RS-T and T-waves, in Leads I and III (figure 1A). When these electrocardiographic abnormalities are present, they are pathognomonic of a coronary artery occlusion.

*Anterior wall infarction* was predicated on the presence of a large  $Q_4$ , and *posterior wall involvement* by large  $Q_2$  and  $Q_3$  with inverted  $T_{2,3}$ , i.e., Lead II and III changes. In other words, a *massive infarction* was present since anterior and posterior walls of the left ventricle were both damaged.

- 2 *A pericarditis* was predicated on the appearance of the RS-T elevations with no depressions in the electrocardiogram (figures 1B and 1C).

3 Septal perforation was diagnosed by the sudden appearance of a thrill and a loud systolic murmur in about the fourth intercostal space, just to the left of the sternum

A septal perforation is found only in *severe coronary disease*,<sup>1, 2</sup> i e, branches of both the left and right coronary arteries are involved. On the other hand, because of the patient's relatively young age, 47, the probability would be that the other blood vessels in the body would be only slightly or moderately involved.<sup>3</sup>

4 The *Bernheim syndrome*,<sup>4</sup> as originally described by Bernheim, connoted a herniation of the septum into the right ventricle due to increased intraventricular pressure in the left chamber. This was evident by the swelling of the neck veins and the absence of marked congestion of the lungs. It was logical to assume that the septum weakened by infarction to the point of perforation would easily give way under the pressure in the left ventricle. The interference with the filling of the right ventricle caused back pressure into the neck veins. Bernheim made the point that marked congestion of the lungs was absent. Probably the explanation of this is that the block in return of venous blood to the right ventricle prevents engorgement of the lungs which one usually sees in ordinary failure of the left ventricle, of which coronary occlusion is a classical example.

5 Diagnosis of *superior vena cava thrombosis* was based on the cyanosis of the head, neck and upper chest above an unusually straight line across the chest at about the level of the second intercostal space, fullness of the veins in this area, the probability of the presence of a mural thrombus on the walls of the septum, and possible radial embolism.

The autopsy report, as done by Lt Comdr J S Shaver, MC, USN, is as follows

#### AUTOPSY FINDINGS

*General* Body is that of a well-developed, well nourished adult, white male about 47 years of age measuring 73 inches in length and weighing approximately 200 pounds. Rigor mortis is absent, body heat is present, and the body is not embalmed. The hair is coarse, straight, and iron gray in color. Several days' growth of beard covers the face and chin. Marked cyanosis is noted about the lips, ears and face. The pupils are regular and equal and measure six millimeters in diameter. The irides are dark gray in color. Numerous gold fillings are present in the teeth. The thyroid gland is not palpable, and there is no enlargement of the cervical glands. The chest is barrel shaped and is bilaterally symmetrical. The abdomen is slightly protuberant, the external genitalia are normal. Several venipuncture wounds are present in the right antecubital fossa.

*Abdominal Cavity* The panniculus adiposus of the anterior abdominal wall is quite abundant and measures three centimeters in thickness. The peritoneal surfaces are smooth and glistening and free of adhesions. The liver is moderately enlarged, with the lower border extending four centimeters below the right subcostal margin. There is much adipose tissue in the mesenteries and the omentum. A small accessory spleen is attached to the hilus of the spleen by a small connective tissue band. The foramen of Winslow is patent, and the abdominal organs are in normal relationship to each other.

*Thoracic Cavity* No fluid is present in either pleural space. However, dense fibrous tissue bands extend between the visceral and parietal apical pleurae on the right side. The pericardial sac is obliterated completely by an adhesive layer of fibrin. The adhered walls are easily separated from each, leaving ragged pericardial and epicardial surfaces. The heart is enlarged. The apex is located 13.4 centimeters

from the mid-sternal line in the sixth intercostal space, left The right border is 5.5 cm from the mid-sternal line in the fifth intercostal space, right

*"Lungs"* The right lung weighs 600 grams and is slightly decreased in size The pleura of the entire upper lobe is bound down by dense fibrous adhesions Crepitus is completely absent in the lower lobe, which is reddish-purple in color The lung parenchyma is very flabby in consistency and there are no areas of consolidation A



FIG 2 This is a photograph of the heart taken at post mortem The chamber of the left ventricle is seen The white arrows show two perforations in the septal wall between the left ventricle and the right (behind) Herniation of the septal wall back into the right ventricle is obvious

large amount of dark serosanguineous fluid drains from the cut surfaces of the organ, especially the dependent areas

"The left lung weighs 595 grams and is also smaller than normal There are a few grayish-white calcified lesions in the apex The lower two-thirds of the organ is grayish-purple in color and is airless Much serosanguineous fluid drains from the cut surfaces of the non-aerated portion of the lung

*"Heart"* The heart is enlarged and in the dissected state weighs 610 grams The enlargement is due to a concentric type of hypertrophy and an associated terminal dilatation of the chambers All epicardial surfaces are dull and covered by a moder-

ately thickened layer of ragged, grayish-white fibrinous exudate. This exudate is easily scraped away by the use of a knife which indicates an unorganized lesion. There is a marked generalized softening and loss of consistency of the entire myocardium. The softening predominates in the apical area of both ventricles, particularly the left chamber. Sections through this infarcted area reveal a mottled myocardium, and the muscle wall in the apical area measures only eight millimeters in thickness. A rather widespread mural thrombus is attached to the wall of the endocardium, and is firmly fixed in situ. Of particular interest is the marked deviation or herniation of the muscular portion of the interventricular septum toward the right side of the heart. The greatest displacement of the pale, necrotic, friable septum toward the right is at least 2.5 cm from its original position. This displacement is so marked that the septum almost touches or lies against the inner surface of the right ventricular wall, with marked encroachment upon the cavity of this chamber. Gentle removal of the septal thrombus in the left ventricle reveals a ragged perforated lesion in the septal wall which is located near the posterior margin of the septum and measures 13 by 6 mm. The edges of the hole evaginate toward the right ventricular cavity. The mural thrombi in the two ventricular cavities are connected with each other by a connecting fibrinous clot through the septal defect. A second smaller perforation is present in the anterior portion of the septum, and white mural thrombus is attached to the atrial wall, and from this mass of partially organized fibrin arises a mixed antemortem or terminal thrombus which passes upwards to enter the lumen of the superior vena cava with marked encroachment upon the lumen. Serial cross sections of the coronary system are made for detail study of the lumen of these vessels. The wall of the left coronary from its aortic orifice to its bifurcation is quite rigid due to calcium salts deposits, and the lumen is quite narrow. The narrowed lumen of the descending branch of the left artery is completely obliterated by a reddish-brown antemortem thrombus which extends from the bifurcation throughout its entire length. Even the branches of the vessel are occluded. The circumflex branch is also occluded by an antemortem thrombus from the level of the bifurcation to a point 3.5 cm below the origin of the vessel. There is a high degree stenosis of the right coronary orifice with the lumen measuring less than 0.5 mm in diameter. Although the lumen of the vessel is narrowed, no thrombi are found in this artery. The cardiac measurements are as follows: Apical left ventricular myocardium, 8 mm, left ventricular myocardium near the base of the heart, 14 mm, right ventricular myocardium, 6 mm, aortic valve, 7.5 cm, pulmonary 8.5 cm, mitral valve, 10 cm, and tricuspid valve, 14.0 cm.

*"Vascular System"* A few atheromatous ulcers and many atheromatous and atherosclerotic plaques are visible in the intima of the abdominal portion of the aorta above the bifurcation of this vessel. The peripheral vessels are hardened and easily palpable. The coronary lesions are described under the paragraph of the heart.

*"Genito-Urinary System"* The right kidney weighs 195 grams after removal of the capsule. Of interest is the position of the origin of the proximal end of the ureter from the pelvis of the organ. The uretero-pelvic junction is situated at a higher level than the normal, and there appears to be an acute angulation of the junction, which produces a kinking deformity. The pelvis appears dilated. The capsule strips with ease from the cortex revealing a moderately smooth cortical surface. No retention cysts are visible, and there is only a minimal stellate scarring. The cortex measures five millimeters in thickness. The calyces and pelvis are moderately dilated, which is apparently due to a mechanical obstruction due to the high take-off of the ureter from the pelvis. The ureteral lumen is of normal size below the uretero-pelvic junction. The left kidney weighs 205 grams and is normal in size and shape. The cortex is similar in appearance to that of the right organ. The calyces, pelvis and ureter are normal. The urinary bladder contains 80 c.c. of clear straw colored urine, and the mucosa is normal. The prostate is soft and normal in size and consistency. The seminal vesicles are not remarkable."

## MICROSCOPIC EXAMINATION

*Heart* Sections through the apical myocardium show areas of coagulation necrosis with complete disappearance of the cell nuclei and vacuolation of the muscle cytoplasm. Adjacent to this recent area of infarction is an area in which the myocardial fibers have been replaced by highly vascularized fibroblastic stroma. Many fat cells are located deeply in the fibrotic myocardium. Partially organized fibrin containing enmeshed red and white cells adheres to the endocardium of both right and left ventricles. Cross sections through both left circumflex and left descending branches of the left coronary show a thickened hyalinized intima infiltrated with calcium salts and cholesterol crystals. The narrowed lumen is filled with a partially organized thrombus. In summary, the heart lesions are representative of coronary thrombosis, with both old and recent infarction of the myocardium supplied by the involved vessels.

*Lungs* Many of the alveolar spaces are filled with fluid and large macrophages containing engulfed degenerated blood pigment. The capillaries of the alveolar septa are dilated and stuffed with blood. The pleural surfaces in the right apical area are thickened by fibrous tissue bands, there is no evidence of pneumonia.

*Final Pathological Diagnoses* Primary Heart Coronary thrombosis (both branches of left artery, i.e., left anterior descending and left circumflex branches) Massive cardiac infarction, recent and old. Diffuse myocardial fibrosis. Fatty infiltration. Ruptured interventricular septum. Deviation of the septum to the right with encroachment upon right ventricular cavity. Mural thrombi, both ventricles. Mural thrombus, right atrium with extension into orifice and lumen of superior vena cava producing superior vena cava stasis. Cardiac hypertrophy and dilatation, 610 grams. Generalized fibrinous pleuritis.

*Secondary* Lungs Fibrous pleuritis, apical, right. Healed apical tubercles, left apex. Hypostatic congestion and edema, marked. Kidneys Chronic passive congestion. Hydronephrosis, right. Mechanical kinking of right ureter (high take-off). General Obesity. Arteriosclerosis, moderate.

*Cause of Death* Coronary thrombosis.

## CONCLUSIONS

The clinical signs, the circulatory dynamics and the electrocardiograms are described which led to an antemortem diagnosis of acute coronary occlusion with massive infarction of the anterior and posterior walls of the left ventricle, pericarditis, perforation of the intraventricular septum, Bernheim syndrome of herniation of the septum into the right ventricle and, finally, superior vena caval thrombosis. The cause of the marked azotemia during the last days of illness was not clear, but was thought probably to be due to renal insufficiency caused by prolonged shock.

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# EDITORIAL

## THIOURACIL

THE introduction of thiouracil as a therapeutic agent constitutes a real advance in the treatment of hyperthyroidism. Although a great deal remains to be learned about the action of the drug, observations which have already been made are sufficient to prove its potency and to indicate some of its limitations and dangers. In this number of the ANNALS OF INTERNAL MEDICINE we are presenting reports regarding the clinical use of thiouracil by Palmer<sup>1</sup> and by Bartels,<sup>2</sup> from the standpoint of the internist and surgeon, respectively.

The clinical use of thiouracil by Astwood<sup>3</sup> and by Williams and Bissell<sup>4</sup> was suggested by investigations in which goiter had been experimentally produced in animals. It had been shown by various observers that the feeding of Brassica seed to animals resulted in the production of goiter. Kennedy,<sup>5</sup> suspecting that the active substance in the seed was a derivative of thiourea, demonstrated that the latter substance was actively goitrogenic. Astwood<sup>6</sup> tested a large number of chemically related substances, and found that thiouracil was the most active of all. The sulfonamides exert a similar but quantitatively less marked effect.

The thyroid glands of animals treated with thiouracil show marked hyperplasia with tall columnar acinar cells, and a diminution of colloid. They are very vascular. The content of iodine and thyroxin is diminished, and they absorb relatively little iodine when the latter is administered. The basal oxygen consumption is diminished. There is a retardation of growth in young animals. Histological changes in the pituitary gland have been described, similar to those which follow thyroidectomy. The pituitary gland is concerned in some way with the action of thiouracil, since the latter does not excite goiter formation in hypophysectomized animals. The most definite direct action of thiouracil, however, is in some way blocking the absorption of iodine by the thyroid and inhibiting the production of thyroxin. It does not inhibit the action of thyroxin which has already been formed or which is administered. The physiological changes which it produces thus resemble those following subtotal thyroidectomy.

In man the effects of thiouracil appear to be similar to those observed

<sup>1</sup> PALMER, M. VIRGINIA. Hyperthyroidism and thiouracil, *Ann Int Med*, 1944, **xii**, 335.

<sup>2</sup> BARTELS, E. C. Use of thiouracil in the preoperative preparation of patients with severe hyperthyroidism, *Ann Int Med*, 1945, **xii**, 365.

<sup>3</sup> ASTWOOD, E. B. Treatment of hyperthyroidism with thiourea and thiouracil, *Jr Am Med Assoc*, 1943, **cxxii**, 78.

<sup>4</sup> WILLIAMS, R. H., and BISSELL, G. W. Thiouracil in the treatment of thyrotoxicosis, *New England Jr Med*, 1943, **ccxxix**, 97.

<sup>5</sup> KENNEDY, T. H. Thioureas as goitrogenic substances, *Nature*, 1942, **cl**, 233.

<sup>6</sup> ASTWOOD, E. B. The chemical nature of compounds which inhibit the function of the thyroid gland, *Jr Pharmacol and Exper Therap*, 1943, **lxxviii**, 79.

in animals. There is cellular hyperplasia of the thyroid, with increased vascularity and diminished colloid. In the manner in which it has been administered in human cases of thyroid disease, however, it has caused relatively little gross increase in the size of the gland. There may be a moderate increase in size, but usually this is transient and is followed by a slow decrease if treatment is continued. The hyperplasia is generally attributed to stimulation by the thyrotropic hormone of the anterior pituitary. The formation and action of the latter is no longer controlled, as it normally is, by thyroxin, since the production of thyroxin by the thyroid has been inhibited. Several observers, including Palmer, have reported favorable clinical results from the administration of small doses of thyroxin or desiccated thyroid with thiouracil. This seems to lessen the tendency both to excessive hyperplasia of the thyroid and to the development of exophthalmos and other ocular disturbances which are also a result of the action of the thyrotropic hormone.

The absorption and elimination of thiouracil and its distribution in the body tissues have been studied extensively by Williams and his associates.<sup>7, 8</sup> It is absorbed rapidly from the stomach and upper part of the small intestine, appearing in the blood in substantial concentration within 15 to 30 minutes. About 15 per cent of therapeutic doses appear to be destroyed before absorption, and none is detectable in the feces. About a third of that administered is excreted in the urine, a large proportion within a few hours. The balance is distributed widely through the body tissues, but in varying concentration, the highest being found in the pituitary, thyroid, adrenals and bone marrow (leukocytes). Most of the circulating thiouracil is concentrated in the red cells. It is altered or destroyed quite rapidly in the tissues, nearly all being eliminated within 24 hours. The drug leaves the blood rapidly, and to maintain a reasonable concentration, the quantity administered daily should be divided into at least three doses.

Williams<sup>9</sup> has recently reviewed the clinical results obtained by the use of thiouracil in about 300 cases, of which 174 were treated by him and his associates, and the others were collected from the literature. From the study it seems clearly established that if the drug is tolerated, the basal metabolic rate can be lowered to the normal range and the clinical symptoms relieved in practically every case, either of diffuse hyperplasia or toxic adenoma. Palmer emphasizes the point that clinical improvement may be well marked after one or two weeks of treatment, before there has been any notable change in the basal metabolic rate. The time required for the rate to reach normal was about five weeks on the average (Williams) or about one day for each per cent of elevation of the basal metabolic rate.

<sup>7</sup> WILLIAMS, R. H., KAY, G. A., and JANDORF, B. J. Thiouracil. Its absorption, distribution and excretion, *Jr Clin Invest*, 1944, **xviii**, 613-627.

<sup>8</sup> WILLIAMS, R. H. Further studies of the absorption, distribution, and elimination of thiouracil, *Jr Clin Endocrinol*, 1944, **iv**, 385.

<sup>9</sup> WILLIAMS, R. H. Antithyroid drugs, with particular reference to thiouracil, *Arch Int Med*, 1944, **lxxiv**, 479.

(Bartels) In patients who had previously had substantial treatment with iodine, a much longer time was required. As the basal metabolic rate falls, the dose is reduced. A small daily maintenance dose is required, but if this is given the effect can be maintained, apparently indefinitely.

It is not yet known whether or how often "cure" may be anticipated, in the sense that there will be no recurrence of hyperthyroidism after treatment is stopped. When treatment has been continued for only a few weeks, relapses have usually occurred. Several patients who had been treated for many months, however, had remained well for several months after treatment was stopped. Others subsequently relapsed.

Bartels' <sup>2</sup> recent work indicates that thiouracil is of great value in preparation of patients for operation. Thiouracil has manifest advantages over iodine in patients who tolerate it, in the relative certainty and indefinite persistence of its action, even though a longer period of preliminary treatment is required. Patients do not "escape" from its effects. The technical difficulties encountered at operation in patients prepared with thiouracil appear to be largely eliminated by administering iodine for a short period before operation, after improvement has been obtained with thiouracil.

The grave drawback to the use of thiouracil, and one which may seriously limit its applicability, is to be found in the toxic reactions which it occasionally produces. Reactions of varying severity have been reported in about 10 per cent of the cases treated, appearing usually during the first five weeks. Among the symptoms noted are fever, cutaneous eruptions, gastrointestinal disturbances, jaundice, edema, enlargement of the salivary glands and lymph nodes, thrombocytopenia, leukopenia and agranulocytosis. Most of these symptoms have subsided promptly after the drug was stopped. In some cases it has been possible to resume treatment later with smaller doses, but in three cases reported fever recurred promptly when a subsequent dose was given. Marrow injury, however, is more serious and may prove fatal if it is not recognized promptly and if agranulocytosis develops. The frequency of this complication is not known, and it will probably vary with the care with which the patients are supervised. Williams observed two cases in 174 cases treated.

Lesser degrees of leukopenia are more common. Palmer observed nine cases in her series, but was able to resume treatment later in all of them, after an intermission. It seems questionable how often this will be possible. In some cases, at least, there appears to be an individual hypersensitiveness to the drug.

Bartels <sup>2</sup> noted three cases of leukopenia among 119 cases, one of whom had mild angina. It is important that in two of these cases, the leukopenia appeared only after protracted treatment (eight and 10 months, respectively) and while receiving small doses of thiouracil (0.6 gm a week, and 0.1 gm every other day). All recovered promptly when the drug was stopped, but no statement was made as to whether a resumption of treatment was attempted.

Another theoretically possible danger is suggested by the observations of Bielschowsky<sup>10</sup>. He found that in rats the administration of thiourea together with a chemical carcinogenic agent (2-acetylaminofluorine) resulted in the development of malignant tumors in the thyroid, although this did not occur if only one of the substances was given. The hyperplastic tissue of the thyroid in human cases treated with thiouracil might be similarly susceptible to the action of intrinsic or extrinsic carcinogenic agents, if such were present.

These facts indicate that thiouracil is a potentially dangerous drug which should not be used at present except in patients who can be closely supervised, particularly with reference to their leukocytes and platelets. Furthermore, this supervision cannot be relaxed after a few weeks or months of treatment, even though the incidence of such reactions is then less. With such care, thiouracil apparently constitutes a reasonably safe and highly effective means of controlling hyperthyroidism, at least temporarily. To what extent it may supplant thyroidectomy in treatment can be determined only after much more study. In cases with adenomata or with a notably enlarged abnormal gland, thiouracil has little effect in reducing the size of the gland, and operation will usually be necessary. In cases with simple diffuse hyperplasia, considerable reduction in size may eventually be obtained. However, we do not yet know the relative mortality in groups of patients treated in these two ways. We do not know what the end result of thiouracil treatment may be, whether it is eventually curative in the strict sense, or whether it must be continued until spontaneous recovery takes place, nor do we know in either case how long this period of treatment must be. There is manifestly need for more investigation, for many more facts. In the meantime, we may hope that some less toxic substitute for thiouracil may be found.

<sup>10</sup> BIELSCHOWSKY, F. Tumors of the thyroid produced by 2-acetylaminofluorine and allylthiourea, *Brit J Cancer Path*, 1944, 22, 90.

## REVIEWS

*The Pathology of Internal Diseases* Fourth Edition By WILLIAM BOYD, M D, LL D, M R C P Ed, F R C P, Lond, Dipl, Psych, F R S C 857 pages, 24 × 15.5 cm 1944 Lea & Febiger, Philadelphia Price, \$10.00

The fourth edition of this volume maintains the standard of excellence achieved by previous editions. Considerable new material has been added including, among others, discussions of disseminated lupus erythematosus, primary atypical pneumonia, Meigs' syndrome, alloxan diabetes, cystic fibrosis of the pancreas, the Rh factor in erythroblastosis fetalis, etc. Throughout the book an effort is made to correlate pathology and pathological physiology with the clinical manifestations of disease. The result is an eminently readable book with not too much of the austerity of the text book. The illustrations are numerous and well chosen. Carefully selected bibliographies are to be found at the end of each chapter. The book can be highly recommended.

M S S

## BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Aids to Clinical Pathology* By DAVID HALER, M B, B S (Hons) Lond, D C P London 358 pages, 16.5 × 10.5 cm 1944 Williams and Wilkins Company, Baltimore Price, \$2.00

*Arterial Hypertension Its Diagnosis and Treatment* By IRVINE H PAGE, M D, and ARTHUR CURTIS CORCORAN M D 352 pages, 21 × 14.5 cm 1945 The Year Book Publishers, Chicago Price, \$3.75

*Familial Susceptibility to Tuberculosis* By RUTH RICE PUFFER, D I P H 106 pages, 21.5 × 14.5 cm 1944 Harvard University Press, Cambridge, Massachusetts Price, \$2.00 (Harvard University Monograph in Medicine and Public Health Number 5)

*Medico-Legal Blood Group Determination* Second Impression By DAVID HARLEY, M D, B Sc, F I C 119 pages, 22 × 14.5 cm 1944 Grune and Stratton, New York Price, \$3.50

*The Avitammoses* Third Edition By WAITER H EDDY, Ph D, and GILBERT DALLDORF, M D 438 pages, 23.5 × 15.5 cm 1944 Williams and Wilkins Company, Baltimore Price, \$4.50

*Patients Have Families* By HENRY B RICHARDSON, M D, F A C P 408 pages, 24 × 16 cm 1945 The Commonwealth Fund, New York Price, \$3.00

## COLLEGE NEWS NOTES

### ADDITIONAL A C P MEMBERS IN THE ARMLD FORCES

Previously reported in the News Notes section of this journal were the names of 1,845 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,855.

Elbert B Agnoi  
Paul H Beigert  
Kelso A Carroll  
Robert K Dixon  
Robert E Driscoll

Hiland L Flowers  
Douglas D Martin  
Frank R Mount  
John F Rainey  
John W Williams

The following members of the College have retired from active military duty and returned to civilian status:

John I Marker, Colonel, (MC), AUS—Davenport, Iowa  
William S McCann, Captain, (MC), USNR—Rochester, N Y  
Thomas P Sharkey, Lieutenant, (MC), USNR—Dayton, Ohio  
Albert Soiland, Captain, (MC), USNR—Los Angeles, Calif  
Samuel A Weisman, Major, (MC), AUS—Los Angeles, Calif

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### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged:

#### *Book*

Leon H Warren (Associate), Lieutenant Colonel, (MC), AUS—"Handbook of Skin Diseases"

#### *Monograph*

Dr Ernest E Hadley, F A C P, Washington, D C—"Military Psychiatry"

#### *Reprints*

Dr Arthur J Atkinson (Associate), Chicago, Ill—2 Reprints  
Dr Robert M Craig (Associate), U S Public Health Service (R)—1 Reprint  
Dr G H Faget, F A C P, U S Public Health Service—1 Reprint  
Dr Paul Gross (Associate), Glenshaw, Pa—1 Reprint  
Dr William E Jahsman, F A C P, Ferndale, Mich—1 Reprint  
Dr Emma S Moss, F A C P, New Orleans, La—1 Reprint  
James S Sweeney, F A C P, Colonel, (MC), AUS—1 Reprint  
Dr Lawrence S Ward (Associate), New London, Conn—1 Reprint

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### NEW LIFE MEMBERS

The following Fellows of the College have recently subscribed to Life Membership and are listed in the order of receipt of subscriptions:

Dr Fred J McEwen, Wichita, Kan  
Dr Victor M Longmire, Temple, Tex

Dr. Irving J. Sands, Brooklyn, N. Y.  
 Dr. John W. Scott, Lexington, Ky.  
 Dr. J. Albert Bauer, Burlington, Ont., Can.  
 Dr. Ivin R. Fox, Eugene, Ore.  
 Dr. Joseph Kopecky, San Antonio, Tex.  
 Dr. Randolph Lyons, New Orleans, La.  
 Dr. Robert G. McCorkle, San Antonio, Tex.  
 Dr. William S. Reveno, Detroit, Mich.  
 Dr. Thomas P. Sprunt, Baltimore, Md.  
 Dr. M. K. Wylder, Albuquerque, N. M.  
 Dr. Arthur C. DeGraff, New York, N. Y.  
 Dr. John Day Garvin, Pittsburgh, Pa.  
 Dr. John Ernest Nelson, Seattle, Wash.  
 Dr. Joseph A. Pollia, Los Angeles, Calif.  
 Dr. Fred Sternagel, West Des Moines, Iowa.  
 Dr. C. Clyde Sutter, Rochester, N. Y.  
 Dr. Chester Q. Thompson, Omaha, Nebr.  
 Dr. Daniel D. Comstock, Los Angeles, Calif.  
 Dr. Elliott P. Smart, Mumphys, Calif.  
 Dr. W. Bernard Yegge, Denver, Colo.  
 Dr. Guy D. Callaway, Springfield, Mo.  
 Dr. Francis M. Pottenger, Jr., Monrovia, Calif.  
 Dr. Thomas E. Strain, Shreveport, La.  
 Dr. Clarence C. Campman, West Middlesex, Pa.  
 Dr. George S. Landon, San Bernardino, Calif.  
 Dr. Roy A. Ouer, San Diego, Calif.  
 Dr. John H. Fitzgibbon, Portland, Ore.  
 Dr. Henry M. Ray, Pittsburgh, Pa.  
 Dr. Samuel Gitlow, New York, N. Y.  
 Dr. Sigurd W. Johnsen, Passaic, N. J.  
 Dr. Franklin Jesse Nelson, Tulsa, Okla.  
 Dr. George R. Maxwell, Morgantown, W. Va.  
 Dr. Homer A. Ruprecht, Tulsa, Okla.  
 Dr. Henry N. Tihen, Wichita, Kan.  
 Dr. Irving L. Cabot, Brooklyn, N. Y.  
 Dr. Jacob M. Cahan, Philadelphia, Pa.

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WAR COMMITTEE ON CONVENTIONS, OFFICE OF DEFENSE TRANSPORTATION,  
CANCELS MEETINGS

The War Committee on Conventions of the Office of Defense Transportation, Washington, has canceled meetings of all character in which the attendance shall be more than 50.

The Regional Meeting of the American College of Physicians for the territory embracing Kansas, Missouri, Nebraska, Oklahoma and Western Texas at Oklahoma City, February 22-23, had to be canceled just two weeks in advance of the meeting, due to delays in receiving final decision from the War Committee on Conventions. The program had been printed and distributed early in January. Many civilian physicians and Medical Officers in the Armed Forces had already obtained their reservations and made their plans for attendance. It was a matter of great disappointment to have to cancel this very excellent program, yet the College gladly joins any movement that will facilitate the more expeditious conduct of the war.

For this same reason, the proposed Regional Meeting of the College at St. Louis, Mo., May 3-4, and an Executive Session of the Regents and Governors, along with the Annual Business Meeting of the College for the election of Officers on May 5, has been canceled. The effect of this is to delay until an appropriate time in the future approved by the Office of Defense Transportation, the election of new Officers, Regents and Governors of the College. In the meantime, the present incumbents will continue in office.

No more regional meetings of the College will be planned until the present transportation and housing emergency is passed.

#### ACP BOARD OF REGENTS WILL MEET IN PHILADELPHIA, JUNE 9-10

The regular spring meeting of the Board of Regents for the conduct of College business and the election of candidates will be held at the College Headquarters in Philadelphia on June 9-10. This meeting, which affects only 20 to 24 men, does not come under the domain of the War Committee on Conventions. The various Committees of the Board of Regents will meet on Saturday, June 9, and the formal meeting of the Board of Regents will take place on Sunday, June 10.

The proposals of candidates for membership must be filed at least 30 days in advance of this meeting if action is desired at this time.

#### ACP SPRING SCHEDULE OF POSTGRADUATE COURSES

In accordance with the recommendation of the Office of Defense Transportation, the registration in each postgraduate course of the College will be restricted to not more than 50 physicians. This will result in the College being unable to accommodate many physicians other than members of the College. Wherever facilities permit, courses will be opened to non-members in the following order: (1) candidates for membership, (2) Medical Officers in the Armed Forces, (3) physicians preparing for examinations by their specialty boards, (4) other non-members having adequate background for advanced work.

The tuition fee for these courses will be \$20.00 per week to civilian members of the College, \$40.00 per week to non-member civilian physicians, free to Medical Officers of the Armed Forces of the United States and Canada.

The courses scheduled are as follows (full outlines of Courses Nos. 1 and 2 appeared in the February Issue of this journal, inasmuch as the detailed Bulletin of the courses has now been published, the outlines of the remaining courses are not herein reprinted, but interested physicians may obtain copies of the Bulletin on request to the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.)

- No. 1—CARDIOLOGY. Columbia University and Presbyterian Hospital, New York, Robert L. Levy, F.A.C.P., Director, one week, March 19-24.
- No. 2—MECHANISMS OF DISEASE. Harvard University and Peter Bent Brigham Hospital, Boston, George W. Thorn, F.A.C.P., Director, two weeks, April 9-21.
- No. 3—CLINICAL MEDICINE—HEMATOLOGY. Ohio State University, Columbus, Charles A. Doan, F.A.C.P., Director, one week, April 16-21.
- No. 4—GASTRO-INTESTINAL DISEASES. Graduate Hospital, Philadelphia, Henry L. Bockus, F.A.C.P., Director, one week, April 23-28.



No 5—APPLICATIONS OF PSYCHIATRY TO THE PRACTICE OF INTERNAL MEDICINE  
University of Wisconsin, Madison, Hans Reese, F A C P, Director, one  
week, April 30-May 5

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#### REGIONAL DINNER MEETING HELD IN LOS ANGELES

A dinner meeting of the Fellows and Associates of the American College of Physicians in Los Angeles and environs was held at Los Angeles on February 23. Dr William D Stroud, F A C P, Treasurer of the College, Professor of Cardiology at the University of Pennsylvania Graduate School of Medicine, was the guest speaker.

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#### A C P MAIL RIFLED

It has been discovered recently that outgoing mail from the College headquarters in Philadelphia to Medical Officers in the Armed Forces has been intercepted and rifled, presumably in the Philadelphia Post Office. Portions of air mail envelopes, with the addresses and the contents removed, have been found, dating back as far as October 20, 1944. There is no adequate means of determining to whom the specific letters were addressed, and, therefore, the College cannot determine whose letters were not delivered. Members whose inquiries have not been answered are requested, under the circumstances, to write again to the Executive Offices of the College. It may be stated that no information of military importance or of any other importance, except to the recipient, has been obtained by those rifling the mail.

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#### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

Lt Col Burgess L Gordon, F A C P, (MC), AUS, of Philadelphia, formerly at the Army Ground and Service Forces Redistribution Station, Asheville, N C, has been assigned to Hospital Division, Operations Service, Office of the Surgeon General.

Major Ramsdell Guiney, F A C P, (MC), AUS, of Buffalo, formerly at the Kansas City Quartermaster Depot, was recently assigned as Chief of the Industrial Medical Program Branch, Occupational Health Division, Preventive Medicine Service of the Surgeon General's Office.

Major General George F Lull, F A C P, Deputy Surgeon General, addressed a forum at the New York Times Hall, January 25, on "Army Nurse Recruitment." In stressing the rising need for nurses he said, "Last month there were over 30,000 patients brought back to the United States hospitals from overseas by airplane and hospital ship. It is my opinion that when this month ends that number will be greater."

Dr Douglas Donald, F A C P, Detroit, College Governor for Michigan, was recently promoted from Major to Lieutenant Colonel, (MC), AUS.

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At a joint meeting of the Jackson Park Branch of the Chicago Medical Society and the Clinical Section of the Chicago Heart Association, on January 18, 1945, the speakers were Dr Chauncey C Maher, F A C P, on "The Heart in the Middle Aged,"

and Dr Howard Wakefield, F A C P "Concerning Certain Problems of Coronary Artery Disease"

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Dr William Dameshek, F A C P, addressed the Puerto Rico Medical Association at its last annual meeting in San Juan in December, 1944. He spoke on the "Physiologic Principles in Anemia" and on "Hemolytic Anemias." He also gave clinics at various hospitals including one at the School of Tropical Medicine in San Juan.

He also visited the Dominican Republic and lectured at the University of Santo Domingo on "Hemolytic Anemias."

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Dr Samuel A. Weisman, F A C P, formerly of Minneapolis, Minn., has been retired from active duty in the Medical Corps of the Army of the United States and is now established in practice at 1136 West Sixth St., Los Angeles. Dr Weisman is also connected with the University of Southern California on a part-time teaching appointment.

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Major Leo V. Schneider, F A C P, (MC), AUS, has been made Chief of Industrial Medicine, New York Port of Embarkation. He recently published an article on "Problem Cases in an Army Industrial Installation" in Military Surgeon, January, 1945, issue.

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Dr Charles W. Dunn, F A C P, Philadelphia, has been promoted to Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine.

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Dr George E. Pfahler, F A C P, Philadelphia, has been elected an Honorary Member of the Section of Radiology of the Royal Society of Medicine in England.

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The Consul General of Cuba, Mariano Escalona, announces that the President of Cuba, Dr Grau San Martin, has granted the honor of the Medalla Oficial, National Order of Merit, Carlos Manuel de Cespedes, to Dr J. C. Geiger, F A C P, San Francisco. President Grau San Martin, a distinguished physician, further cites Dr Geiger "as a talented physician and scientist, humanitarian and loyal friend of Cuba and other Spanish American countries."

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Colonel A. N. Ferguson, F A C P, reports a splendid War-Time Graduate Medical Meeting held at the Oliver General Hospital, Augusta, Ga., January 26, 1945. The lectures were chosen largely from the faculties of Emory University School of Medicine, Atlanta, and the University of Alabama School of Medicine. Dr Glenville Giddings, F A C P, Atlanta, local Chairman, arranged the meeting. A vote of appreciation was received from the entire staff of the Oliver General Hospital.

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#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 3 (New York)—Dr O. R. Jones, Chairman, Dr N. Jolliffe, Dr H. W. Cave

*Induction Center, Grand Central Palace, New York, New York*

March 16 Early Diagnosis of Syphilitic Heart Disease—Dr Edwin P Maynard, Jr  
 March 23 (to be repeated on April 6) Report on Anesthesia Practices in the Present War—Dr E A Rovenstine

April 13 (to be repeated on April 20) Common Wartime Dermatoses—Dr Frank C Combes

• April 27 Common Allergic Manifestations—Dr Joseph Harkavy

REGION No 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr B P Widmann, Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

March 23 Surgical Technique in Acute Appendicitis—Dr George Muller

April 6 Surgical Conditions Affecting the Knee Joint—Dr Paul Colonna

REGION No 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr J A Lyon, Chairman, Dr C R Edwards, Dr C B Conklin

*Station Hospital, Fort Belvoir, Virginia*

March 26 Seasonal Hay Fever—Dr Grafton Tyler Brown

*Newton D Baker General Hospital, Martinsburg, West Virginia*

March 19 Experiences with Malaria—Colonel Paul F Russell

Diagnosis of Diarrheal Diseases—Lieutenant Colonel Hardy Kemp

April 2 Management of Plastic Surgery Problems in War—Dr Edward A Kitlowski

Clinic in General Surgery—Dr William F Rienhoff, Jr

April 16 Psychosomatic Medicine—Dr Claude L Neale

Recent Developments in Nutrition—Dr J C Forbes

*A A F Regional Hospital, Langley Field, Virginia*

March 30 Preservation and Restoration of Function of the Extremities—Dr W T Graham

Psychiatry—Dr R Finley Gayle

April 27 Psychosomatic Medicine—Dr Solomon Katzenelbogen

Radiology—Dr Frederick M Hodges

REGION No 8 (Western Pennsylvania, Ohio)—Dr C A Doan, Chairman, Dr P G Smith, Dr F M Douglass

*A A F Regional Station Hospital, Patterson Field, Fairfield, Ohio*

March 21 The Diagnosis and Treatment of the Common Arthritides—Dr Russell Haden

*Critch General Hospital, Cleveland, Ohio*

March 27 Problems in the Diagnosis and Management of Coronary Artery Disease—Dr R W Scott

April 24 Congenital Anomalies of the Genitourinary Tract—Dr William E Lower

REGION No 14 (Indiana, Illinois, Wisconsin)—Dr W O Thompson, Chairman, Dr N C Gilbert, Dr W H Cole, Dr W D Gatch, Dr R M Moore, Dr H M Baker, Dr E R Schmidt, Dr E L Sevringhaus, Dr F D Murphy

*Station Hospital, Camp McCoy, Wisconsin*

- March 28 Allergic States—Dr Theodore L Squier  
 April 11 Effects of Cold and Dampness—Lt Col Irving S Wright  
 April 25 Heart Disease—Dr Chester M Kurtz

*Station Hospital, Triun Field, Wisconsin*

- March 28 Peripheral Vascular Diseases—Dr Geza de Takats  
 April 11 Blood Dyscrasias—Dr Frederick W Madison  
 April 25 Diseases of the Kidneys, Uro-genital Tract—Dr Francis D Murphy

*Gardner General Hospital, Chicago, Illinois*

- March 28 Burns and Plastic Surgery  
 April 11 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment  
 April 25 Endocrinology

*Station Hospital, Fort Sheridan, Illinois*

- March 28 Endocrinology  
 April 11 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment  
 April 25 Psychosomatic Medicine

*Mayo General Hospital, Galesburg, Illinois*

- March 28 Psychosomatic Medicine  
 April 11 Wound Healing and Tendon Surgery  
 April 25 Mental Hygiene and the Preventive of Neuroses in War

*Vaughan General Hospital, Illinois*

- March 28 Mental Hygiene and the Prevention of Neuroses in War  
 April 11 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases  
 April 25 Peptic Ulcer, Gall Bladder and Liver Diseases

*Station Hospital, Camp Ellis, Illinois*

- March 28 Peptic Ulcer, Gall Bladder and Liver Diseases  
 April 11 Low Back Pain  
 April 25 Chest Diseases and Diseases of the Larynx

*Station Hospital, Chanute Field, Illinois*

- March 28 High Blood Pressure  
 April 11 Brain and Spinal Cord Injuries  
 April 25 Conditions Affecting Glucose Metabolism

*Billings General Hospital, Fort Benjamin Harrison, Indiana*

- March 28 Conditions Affecting Glucose Metabolism  
 April 11 Plexus and Peripheral Nerve Injuries  
 April 25 Diseases of the Intestinal Tract—Medical X-Ray and Surgical Diagnosis and Treatment

*Wakeman General Hospital, Camp Atterbury, Indiana*

March 28 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care

April 11 Burns and Plastic Surgery

April 25 Dermatological Diseases

REGION No 24 (Southern California)—Lt Comdr G C Griffith, Chairman, Capt H P Schenck, Dr J F Churchill, Dr W A Morrison

*Birmingham General Hospital, Van Nuys, California*

March 28 Coccidioidomycosis—Drs E M Butt and Ray A Carter

*Station Hospital, Camp Cooke, California*

March 21 Orthopedic Surgery—Lieutenant Colonel R B McGovney and Lieutenant Commander H B Macey

*U S Naval Hospital, Oceanside, California*

March 22 Thoracic Surgery—Dr John Jones and Lieutenant Commander J E Dailey

*U S Naval Hospital, Long Beach, California*

March 17 Diabetes—Drs J W Shearill and Howard F West

*U S Naval Hospital, Corona, California*

March 22 Comparison of Protozoal and Bacillary Dysenteries—Dr John Kessel

*A A F Regional Hospital, Santa Ana, California*

March 20 Plastic Surgery—Lieutenant Commander G H Gray and Dr William S Kiskadden

*Hoff General Hospital, Santa Barbara, California*

March 21 Orthopedic Surgery—Lieutenant Colonel R B McGovney

*March Field, Riverside, California*

March 20 Psychosomatic Medicine—Dr H Douglas Eaton

*Toiney General Hospital, Palm Springs, California*

March 20 Penicillin, Recent Developments in Surgical and Public Health Antisepsis—Dr Frederick Moore

*Station Hospital, U S Naval Air Station, North Island, San Diego, California*

March 16 Internal Derangements of the Knee—Dr John Wilson

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Dr R Bryan Grinnan, F A C P, Norfolk, has been elected a Vice-President of the Seaboard Medical Association

Dr Walter L Nalls, F A C P, Richmond, Va, was recently promoted to Lieutenant Colonel, (MC), U S Army

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Dr D C Wilson, F A C P, of the University of Virginia, has been appointed Chairman, and Dr Frank H Redwood, F A C P, Norfolk, has been appointed a member of the Mental Hygiene Committee of the Medical Society of Virginia, of which Dr H B Mulholland, F A C P, is President

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Dr Oscar Swineford, Jr F A C P, Charlottesville, Va, has been elected President of the American Academy of Allergy Dr John W Thomas, F A C P, and Dr W Randolph Graham, F A C P, both of Richmond, have been elected a Fellow and a member, respectively, of the Academy

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Lt Col Charles M Caravati, F A C P, Richmond, who has for a considerable period of time been at the Percy Jones General Hospital, Battle Creek, Mich, was recently assigned to duty as Chief of Medical Service, Woodrow Wilson General Hospital, Staunton, Va

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#### CLINICAL RESEARCH MEETING

The New York Academy of Medicine will hold a meeting Wednesday evening, May 16, to provide a forum in which research workers of New York City and vicinity may present results of original research in clinical medicine

This meeting is being arranged by the Committee on Medical Education of the Academy in view of the dearth of meetings of national medical societies before which research work has usually been presented

Presentations will be limited to twelve minutes A brief period of free discussion will follow each presentation The publication of presentations is not a necessary condition but the Academy plans to publish in the *Bulletin*, abstracts of presentations if the author so desires The fact that material has in substance or in part been presented elsewhere will not be regarded as a bar to presentation, provided that the work represents recent research

The Committee extends an invitation to all research workers of Greater New York and neighboring cities within a radius of one hundred miles, to submit abstracts, not to exceed two hundred words in length, of proposed presentations to the Secretary of the Committee on Medical Education of the Academy, 2 East 103 Street, New York City 29, not later than April 5, 1945 A formal invitation to participate in this program will then be extended by the Committee to the authors of papers selected for presentation

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Colonel Howard A Rusk, F A C P, Chief, Convalescent Training Division, Office of the Air Surgeon, delivered the sixth Frank Billings Lecture of the Thomas Lewis Gilmer Foundation of the Institute of Medicine of Chicago, February 12, his subject being "Rehabilitation—The Challenge to American Medicine"

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Brigadier General James S Simmons, F A C P, Chief, Preventive Medicine Service, Office of the Surgeon General, U S Army, has recently been appointed by the Regents of the University of Michigan as non-resident lecturer in the School of Public Health

Lieutenant Colonel Leon H Warren (Associate), formerly of Philadelphia, has been appointed a member of the National Research Council to represent the War Department in the Division of Medical Sciences

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Dr Harry P Ross (Associate), President of the Richmond (Va) Board of Health, has been appointed a member of the Virginia State Board of Health

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The Abbott Laboratories, Chicago, has made a grant of \$1,800 00 to the Department of Internal Medicine, University of Texas Medical School, Galveston, for the support of research work by Dr Charles T Stone, F A C P, Professor of Internal Medicine

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Dr Noble Wiley Jones F A C P, for a number of years a Regent of the American College of Physicians, was honored on December 14 by the Portland Academy of Medicine, which dedicated its annual dinner meeting to his years of service to the Academy Dr Laurence Selling, F A C P, Professor of Medicine and Neurology, and Dr Homer P Rush, F A C P, Associate Clinical Professor of Medicine, University of Oregon, discussed Dr Jones' contribution to scientific medicine and to the practice of medicine, respectively, while Olof Larsell, Sc D, Professor of Anatomy, discussed his contributions to medical education Dr Jones has served both as Secretary and President of the Portland Academy of Medicine and he is now a member of the Committee appointed to form the Medical Research Foundation of the Academy, designed to aid medical research in the vicinity

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Dr Herbert L Bryans, F A C P, Pensacola, is Chairman of the Medical Advisory Committee of the Florida State Rehabilitation Service Dr Rollin D Thompson, F A C P, Orlando, is a member of the Committee

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Dr Bruce K Wiseman, F A C P, has succeeded Dr Charles A Doan, F A C P, as Chairman of the Department of Medicine, Ohio State University College of Medicine Dr Doan was recently named Dean Dr Wiseman graduated from Indiana University School of Medicine in 1928, and has been a member of the Ohio State University faculty since 1930 In 1939 he was named Professor of Medical Research

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Dr Harold D Palmer, F A C P, was elected on January 12 a member of the Council of the Philadelphia Psychiatric Society

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Dr George D Gammon, F A C P, was recently elected to the Council of the Philadelphia Neurological Society

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Dr Pascal F Lucchesi (Associate), formerly of Philadelphia, has been promoted from Major to Lieutenant Colonel in the Medical Corps of the Army of the United States

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Dr Walter E Vest, F A C P, Huntington, W Va, was elected Chairman of the Board of Trustees of the Southern Medical Association at its last annual meeting in St Louis during November

Dr M E Winchester, F A C P , was recently elected Vice President of the Glynn County (Ga ) Medical Society

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Dr Marion F Beard, F A C P , and Dr Frank A Simon, F A C P , both of Louisville, were recently elected First Vice President and Treasurer, respectively, of the Jefferson County (Ky ) Medical Society

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Dr Raymond O Muether, F A C P , St Louis, is Secretary of the Missouri Medical Service, a plan sponsored by the Missouri State Medical Association .

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Dr Wann Langston, F A C P , Oklahoma City, was recently promoted from Professor of Clinical Medicine to Professor of Medicine and Chairman of that department, University of Oklahoma School of Medicine

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Dr Philip H Jones, Jr , F A C P , New Orleans, has been elected First Vice President of the Orleans Parish Medical Society

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Dr L Emmett Madden, F A C P , Columbia, is President of the Columbia (S C ) Medical Society

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The War Time Graduate Medical Meetings were resumed at the Station Hospital, Camp McCoy, Wisconsin, on February 14, 1945, with Dr Armand J Quick of Marquette University, Milwaukee, as the guest speaker His subject was "Thrombosis, Thrombophlebitis and Anticoagulants "

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Dr James J Waring, F A C P , Denver, has announced that a War-Time Graduate Medical Meeting was held in Denver, Thursday, Friday and Saturday, March 15-17, with the approval of the Office of Defense Transportation The first day's program was held at the Fitzsimons General Hospital The program of the second and third day was held at the Colorado General Hospital Among guest speakers were Dr Cyrus C Sturgis, F A C P , Professor of Medicine, University of Michigan, Dr George W Thorn, F A C P , Professor of Medicine, Harvard Medical School, Colonel Harry Plotz, (MC), of the Army Medical School, Washington, D C , and Colonel Edgar V Allen, F A C P , Consultant to the Seventh Service Command, Omaha, Nebraska

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#### SOCIAL HYGIENE AWARD TO GENERAL IRELAND

Major General Merritte W Ireland, F A C P , former Surgeon General of the U S Army, received the William Freeman Snow Award on February 7, in Chicago This Award was established in 1937 by the American Social Hygiene Association, "For Distinguished Service to Humanity " Announcement of the 1945 Award was made by General John J Pershing, the General of the Armies, acting in his capacity as Chairman of the Association's Committee on Awards

General Ireland's brilliant career began in 1891 as a pioneer Army Medical Officer and culminated in his distinguished service as Surgeon General of the Army, a post which he held from 1918 until his retirement in 1931 During his term of service he reorganized the Surgeon General's Office on the strength of experience



gained during World War I and laid the basis for the present efficient Army medical program through the establishment of the Field Service School at Carlisle Barracks, Pa., and the development of the Army Medical Center at Washington, D. C., and of Army hospital facilities

"In the years since his retirement," said General Pershing, "General Ireland has served civilian as well as military health and welfare with unabated zeal and statesmanship"

The following promotions were announced by the Office of the Surgeon General of the Army, on February 15: From Lieutenant Colonel to Colonel—Benjamin J. Birk, (MC), F. A. C. P., Thiensville, Wisconsin, from Major to Lieutenant Colonel—George Francis Evans, (MC), F. A. C. P., Clarksburg, West Virginia, Hyman Abraham Slesinger, (MC), F. A. C. P., Windber, Pa., Augustus Henry Clagett, Jr., (MC), (Associate), Philadelphia, Pa., Harold Patrick McGan, (MC), (Associate), Albany, N. Y., and Pascal Francis Lucchessi, (MC), (Associate), Philadelphia, Pa.

Colonel John B. Youmans, (MC), F. A. C. P., has resumed his duties as Director of the Nutrition Division, Preventive Medicine Service, Office of the Surgeon General, after a tour of duty in China, where he was engaged in a joint study on the nutrition of Chinese troops

Dr. Chester N. Frazier, F. A. C. P., Professor of Dermatology at the University of Texas Medical School, has been appointed Civilian Consultant to the Surgeon General of the Army in the field of Dermatology. Dr. Frazier acquired wide experience in this field during the many years he lived in China, where he was Head of the Division of Dermatology at Peiping Union Medical College from 1922 to 1943. During World War I Dr. Frazier served as a First Lieutenant in the Medical Reserve Corps.

Lt. Comdr. Fred W. Modern, (MC), U. S. N. R., F. A. C. P., was appointed chief of Medicine, U. S. Naval Hospital, Astoria, Oregon, on Nov. 27, 1944.

The New York Post-Graduate Medical School and The American Academy of Allergy offer a Symposium for Specialists in Allergy, five days, February 26 to March 2, 1945, fee \$100. Applications and inquiries should be addressed to the Director of the School, 309 East 20th Street, New York 3, N. Y.

#### OUTLINE OF COURSE

##### MORNING SESSIONS

Monday, February 26

- 9 00-10 30 Management of the Allergic Clinic Patient  
Dr. SPAIN
- 10 45-12 15 Chemistry of Antibody and Antigen  
Dr. HOOKER

Tuesday, February 27

- 9 00-10 30 Pediatric Allergy  
Dr. CHOBOT
- 10 45-12 15 The Antibodies Concerned in Skin Sensitive Allergies  
Dr. COOKE

Wednesday, February 28

- 9 00-10 30 Critical Discussion of Skin Testing  
DR WALZER  
10 45-12 15 Pharmacology of Drugs Used in Allergic Conditions  
DR BRUGER

Thursday, March 1

- 9 00-10 30 Immunological Problems in Blood Transfusion in Man  
DR LEVINE  
10 45-12 15 Skin Testing in Allergic Dermatoses  
DR SULZBERGER

Friday, March 2

- 9 00-10 30 Autopsy Findings in Bronchial Asthma  
DR GAY  
10 45-12 15 Periarthritis Nodosa and Allergy  
DR ALEXANDER

#### AFTERNOON SESSIONS

The afternoon sessions are to be devoted entirely to colloquia, held in the participating hospitals and concerned with the following particular phases of allergy

Skin Sensitive Asthma  
Infective Asthma  
Nasal Allergy, Hay Fever and Allergic Coryza  
Gastrointestinal Allergy, Urticaria and Angioneurotic  
Edema  
Cutaneous Allergy

## OBITUARIES

## DR JAMES LEWIS WINEMILLER

Dr James Lewis Winemiller, F A C P, of Great Neck, New York, died at the age of 45 on October 1, 1944. Dr Winemiller practiced in Great Neck, New York, he received his Bachelor's Degree from Fordham University and graduated from Cornell University Medical College in 1920, thereafter he spent two years interning in the Lenox Hill Hospital, in later years he specialized in pediatrics.

Dr Winemiller was attending pediatrician, Nassau Hospital, visiting pediatrician, St Francis Sanatorium for Cardiac Children, member, Nassau County Medical Society, Medical Society of the State of New York, Associated Physicians of Long Island and the American Academy of Pediatrics, fellow, American Medical Association and the American College of Physicians, diplomate, American Board of Pediatrics. His untimely death is a serious loss to the profession.

ASA L. LINCOLN, M D, F A C P,  
Governor for Eastern New York

## DR ALFRED M GOLTMAN

Dr Alfred M Goltman, F A C P, died at the Baptist Hospital in Memphis November 11, 1944. He was 49 years old.

In his death the medical profession of Memphis has lost a real friend who stood for the best there is in Medicine, a well trained physician and an excellent teacher. He received his medical degree from Columbia University and was a Resident at Mt Sinai Hospital, New York. In returning to Memphis he was very fortunate in being able to practice with his father, Dr Max Goltman, who was one of the leading physicians of the South.

His work was limited to internal medicine and he was especially interested in Allergy.

As an Associate Professor of Medicine in the Medical School of the University of Tennessee he became very popular among the students because of his sincere efforts and skill in teaching them.

Dr Goltman was a member of the American Medical Association, a Fellow in the American College of Physicians, a member of the American College of Allergists, the Association for the study of Allergy and the Southern Medical Association. He was a diplomate of the American Board of Internal Medicine, with additional certification in Allergy.

WM C CHANEY, M D, F A C P,  
Governor for Tennessee

## DR H BURNS MARVIN

Dr H Burns Marvin, F A C P, died June 20, 1944. He was born in Springwater, Livingston County, N Y, in 1879, graduated in medicine at

the University of Buffalo School of Medicine His internship was spent at the Minnequa Hospital, Pueblo, Colo , from 1907 to 1908

Dr Marvin practiced medicine in Binghamton, N Y , and for many years was attending physician at the Binghamton City Hospital and the Susquehanna Valley Home He was former treasurer and former president of the Broome County Medical Society, former secretary and former president of the Binghamton Academy of Medicine, and for several years served as secretary for the 6th district branch of the New York State Medical Society He was a Fellow of the American Medical Association, and a Fellow of the American College of Physicians since 1928

Dr Marvin was in active practice up to the time of his pneumonia Although he had not enjoyed good health for several years prior to his passing, he felt a responsibility to his community and to his fellow colleagues, and took more than his share of the burdens of the practice of medicine His death removes from the community a distinguished physician and a fine Christian gentleman

RONALD L HAMILTON, M D , F A C P

#### DR JOHN KERR PEPPER

Dr John Kerr Pepper, F A C P , Winston-Salem, N C , died October 31, 1944, at the age of 67, of heart disease and pneumonia Dr Pepper was born June 9, 1877, and attended Guilford College in North Carolina prior to undertaking his medical education He studied medicine at the College of Physicians and Surgeons in Baltimore, Md , and received his medical degree from that institution in 1907 Following his graduation he was, for a time, located in Baltimore where he served as Gastro-enterologist at the Mercy Hospital and Roentgenologist at the University of Maryland Hospital Moving to Winston-Salem, he was for a number of years Roentgenologist for the North Carolina Baptist Hospital Dr Pepper was active in civic affairs in the city of Winston-Salem He was a Charter Member of the Kiwanis Club and served as Lieutenant Governor of the Third District of the Kiwanis International

Active in medical circles, he was a member of the Forsyth County Board of Health, served as President of the Forsyth County Medical Society, President of the North Carolina Radiological Society and First Vice-President of the North Carolina State Medical Society He was a Fellow of the American Medical Association, and at the time of his death was a member of the North Carolina Board of Nurses Examiners

Dr Pepper became a Fellow of the American College of Physicians in 1930, and from the time of his association with the College he was an active and loyal member, was a regular attendant at its meetings and always maintained an abiding interest in the welfare of the College A man of great personal charm, his friends were legion He was a useful, friendly and kindly man and he will be sorely missed by his many friends throughout his native state

PAUL F WHITAKER, M D , F A C P ,  
Governor for North Carolina

## COLONEL BROOKS COLLINS GRANT

Colonel Brooks Collins Grant, Medical Corps, United States Army, died of a cerebral hemorrhage, January 1, 1945, at his home in San Antonio, Texas. Colonel Grant had been a Fellow of the American College of Physicians since 1932.

Born September 10, 1890, at Denton, Texas, Colonel Grant attended Fort Worth and Texas Christian Universities. He received his M.D. degree from the Chicago College of Medicine and Surgery in 1915. During his undergraduate days, he was an instructor at Fort Worth University (1910-11), and at the Fort Worth School of Nursing (1912-13). After being graduated from medical school, he returned to Texas to practice medicine and surgery and was for several years County Health Officer in Big Lake, Reagan County.

Colonel Grant entered the Army as a First Lieutenant in 1917 and was graduated from the Army Medical School, Washington, D. C., in 1920. He had numerous important assignments in the Army Medical Corps during his career, including chief of laboratory, Sternberg General Hospital, chief of laboratory, Walter Reed General Hospital, ward officer, Station Hospital, Fort Sam Houston. During the current war, he served as Commanding Officer of the 34th Evacuation Hospital at Camp Barkeley, Texas, from 1941 to 1942, and was Corps Surgeon of the 13th Corps at Providence, Rhode Island, from 1942 to 1943. While on an overseas assignment in the European theater in the summer of 1944, he became ill and in the fall entered Walter Reed General Hospital, Washington, D. C., as a patient. At the time of his death, he was on sick leave for the Christmas Holidays.

Colonel Grant was interred at the National Cemetery, Fort Sam Houston, Texas. He is survived by his widow, Mrs. Ruth Grant, and a daughter, Miss Gladys Grant, who reside at 142 Harrigan Court, San Antonio, Texas.

Furnished by Technical Information Division

Office of the Surgeon General, U. S. Army

## DR. MORTIMER WARREN

Dr. Mortimer Warren died suddenly at his home at Cape Elizabeth, Maine, on October 8, 1944. His place among his colleagues will be hard to fill. He spent a full and resultant life as a clinical pathologist, bringing to the practice of his profession scientific ardor and a great love of his fellow men.

Dr. Warren was born on December 17, 1873, at Cumberland Mills, Maine, the son of John and Harriet Brown Warren. He was graduated from Bowdoin College in 1896, entered Johns Hopkins and took his medical degree there in 1900. After graduation he studied in Germany during 1902. As assistant clinical pathologist, he began his medical career at Cornell Medical School in New York City from 1902 to 1910, and served as pathologist at Roosevelt Hospital from 1910 to 1916.

In June, 1917, he was commissioned in the Medical Corps of the United States Army and served at Fort Benjamin Harrison and Fort Pike in this country. In November, 1918, he went abroad with Base Hospital 100 to be stationed at Savenay, France, where in March 1919, he was made chief of the medical services, and then commanding officer of the Unit. Returning to this country in August, 1919, he was honorably discharged as a Lieutenant Colonel in the Medical Reserve Corps, United States Army.

In 1920, coming to Portland to practice he became pathologist at the Children's Hospital, and in 1922 began his work at the pathological laboratory of the Maine General Hospital. In November, 1932, he took full charge of the Hospital's new pathological laboratory.

Dr. Warren foresaw the need of medical preparation to the present war. Active in the Civilian Defense preparations he worked to prepare a blood bank in the hospital to be available for any civilian emergency. This was in addition to his participation in the success of the Red Cross blood bank for the Armed Forces.

In recent years, Dr. Warren put his energies and solicitude into the creation of a tumor clinic at the Maine General Hospital. Likewise he took an active part in the Women's Field Army for the Study and Control of Cancer. He was chairman of the Cancer Committee of Maine Medical Association since the establishment of the Committee.

In Maine, Dr. Warren headed the Infantile Paralysis Commission during 1929 and 1930, created by Governor Tudor Gardiner to study and control the disease in Maine.

In 1931, Bowdoin College made him an honorary Doctor of Science on the 35th anniversary of his graduation. He was an active member in the Committee of Physicians. Dr. Warren was also a member of the Cumberland County Medical Society, Innominate Club, Portland Medical Club, American Medical Association, the New England Pathological Association, the New England Cancer Society, the American Society of Clinical Pathologists, the Society for the Study of Internal Secretions. He was a life member of the American College of Physicians and a Diplomate of the American Board of Pathology. His scientific achievements were recognized by publication of his biography in the Directory of American Men of Science. He was an honorary member of Rotary International.

In 1906, he married Mary Pendexter of Bath, Maine, who died in 1911, at the birth of their son John P., who is now a corporal in the Army Air Forces, at Hobbs, New Mexico. He married Pascia Personya of Hartford, Connecticut, in 1914, who survives him. A son of this marriage, Lieut. M. P. Warren, is also in the Army Air Forces, stationed at Walker Field, Victoria, Kansas.

RICHARD S. HAWKES, M.D., F.A.C.P.,  
Acting Governor for Maine

## DR ESTES NICHOLS

Dr Estes Nichols, M D , F A C P , 70, died at his home in Portland, Maine, December 12, 1944, after several months illness

He was born in Boston, Mass , August 10, 1874, the son of Austen Leroy and Josephine Bond Nichols . He attended Bates College and was graduated from the University of Vermont Medical School in 1900 . He was in Public Health and Marine Hospital Service until 1902, when he came to Portland to begin general practice

Dr Nichols served in the Army Medical Corps in the Spanish-American War and in World War I, attaining the rank of Colonel . In World War I, he became a Consultant of Lung Diseases at the Department Headquarters at Boston, and was later Director of the School of Lung Diseases at the Army Medical School, Washington, D C , Director of the School of Internal Medicine, Fort Oglethorpe, Ga , and Commander of General Hospital No 16, at Allentown, Pa

He was a member of the Cumberland County Medical Society, the Maine Medical Association, the American Medical Association, the American Clinical and Climatological Association, and a charter member of the American Tuberculosis Association . He was Vice President of the Maine Public Health Service several years, a member of the National Rehabilitation Committee of the American Legion, special consultant of the U S Veteran's Bureau and Chairman of the Rehabilitation Committee of the First District . He served eleven years as Superintendent of the Maine State Sanatorium at Hebron . He had been a Fellow of the American College of Physicians since 1928, and was a Diplomate of the American Board of Internal Medicine

He is survived by his widow, the former Charlotte Woodman Flint of Dover-Foxcroft, and one son, Estes Flint Nichols, now with the U S Infantry in France

RICHARD S HAWKES, M D , F A C P ,  
Acting Governor for Maine

## DR PETER IRVING

Dr Peter Irving, F A C P , New York, died on December 28, 1944, at Roosevelt Hospital after an illness of several months . He was born in Madison, Wisconsin, in 1878, and was a direct descendant of Peter Irving, who was a brother of Washington Irving . Dr Irving received his A B degree from Columbia University and his M D from the College of Physicians and Surgeons, Columbia University, and, during his early career, was on the teaching staff of Columbia University Medical College . He was on the staff of the Roosevelt Hospital, the City Hospital, and was formerly an Associate Attending Physician at The New York Hospital . For many years he was Assistant Secretary of the Medical Society of the County of New York and, in 1937, became Secretary of the Medical Society of the

State of New York, an appointment which he held until the time of his death. He was a member of the House of Delegates of the A M A, and Fellow of the New York Academy of Medicine, Fellow of The American College of Physicians, and at his death was Consulting Physician at several New York hospitals.

In 1943 he was appointed by the Governor of the State of New York as a member of a Commission to investigate the management and affairs of the Department of Mental Hygiene of the State of New York. Report of this Commission was submitted in 1944 under the title "The Care of the Mentally Ill in the State of New York."

Through the latter part of 1941 and during 1942 he rendered very valuable assistance to the Procurement and Assignment Service for physicians of New York State, and for this he received a citation. He was a tireless worker and gave unstintingly of his time to his fellow men. His chief interests were for his fellow physicians in the State of New York and his passing is a very severe and keenly felt loss.

ASA L. LINCOLN, M D, F A C P,  
Governor for Eastern New York

#### DR. ESMONDE B. SMITH

Dr. Esmonde Bathgate Smith (Associate, 1921), of Brooklyn, New York, died February 2, 1945, at the age of 58.

Dr. Smith graduated from the Cornell University Medical College in 1909, and for a great many years had been the Attending Pathologist to the Methodist Hospital of Brooklyn. His work was restricted to Pathology and Clinical Pathology. He was a member of the New York State Society of Pathologists, the Brooklyn Society of Internal Medicine, the Kings County Medical Society, the Medical Society of the State of New York, and the American Medical Association.

#### DR. EUGENE JOHN LUIPPOLD

Dr. Eugene John Luippold, M D, F A C P, born in Brooklyn, New York, July 22, 1886, for thirty-six years a practising physician in North Hudson, New Jersey, died at his home in Weehawken, December 16, 1944, of melanocarcinoma.

Dr. Luippold attended Northwestern University and received his medical degree from Baltimore Medical College in 1907. After several years of general practice he was appointed pathologist at the North Hudson Hospital, 1919-23, and then became attending physician at the same institution, 1923-27. Since 1927 he had been attending physician at Christ Hospital, Jersey City. He was a past president of the Hudson County Medical Society, a member of the Medical Society of New Jersey, a Fellow of the American Medical Association and the New York Academy of Medicine, and had been a Fellow of the American College of Physicians since 1928.



Dr Luippold was a man of quiet demeanor, reserved, unassuming, yet possessed of a large knowledge of and interest in medical, hospital, civic and community affairs. He was a member of the North Hudson Chamber of Commerce, a director of the First National Bank of Union City, and a former president of the Union City Rotary Club. He was exceptionally well read, and his talks were frequently interspersed with humorous and knowing anecdotes from both classic and modern literature. On a trip to Nice in 1937, as a delegate to the Rotary International, he glimpsed the gathering war clouds and the jeopardy of world peace. His interest and activities in medical spheres were comprehensive and enlightened by travel and serious thought.

In 1910 Dr Luippold married Anna Buchtenkirk. There are two children: a son, Captain Eugene Luippold, serving in the Medical Corps, U S A, now in France, and a daughter, Helen, wife of Major J Reed, U S M C, of East Orange, now stationed at Camp Lejeune, New River, North Carolina.

His death is deeply regretted by all his New Jersey associates

EDWARD A CANNON, M D ,

North Bergen, New Jersey

### DR WILLIAM F CONFAIR

Dr William F Confair, F A C P, of Benton, Pa, died in the Geisinger Hospital, Danville, Pa, on January 14, 1945. Dr Confair was born in Benton on September 22, 1908. He received both his academic and medical training at the University of Pittsburgh, receiving his M D degree in 1932. His internship was served in St John's General Hospital in Pittsburgh.

He took an active and leading part in medical affairs in his community, being on the staffs of the Bloomsburg (Pa) Hospital, the Nanticoke (Pa) Hospital and the Berwick (Pa) Hospital. He was at one time President of the Columbia County Medical Society, a member of his State Society and the American Medical Association. Since 1941 he had been a Fellow of the American College of Physicians.

He entered the Medical Corps of the U S Army in December, 1940, as a Captain and was subsequently promoted to Major. While serving in the Aleutians he sustained serious injuries, which led to his being placed on the inactive list late in 1943. His death was the result of complications arising out of these injuries.

We record with deep regret the loss of this able young physician who gave so much to the public service.

THOMAS M McMILLAN, M D, F A C P,

Acting Governor for Eastern Pennsylvania

## DR FRANCIS JOSEPH DEVER

Dr Francis Joseph Dever, F A C P , died December 30, 1944, in Philadelphia, Pa , at the age of 65 For many years Dr Dever was Internist, and since 1935 Internist Emeritus, to St Luke's Hospital, Bethlehem, Pa , where he practiced his profession for many years

He was a member of the Northampton County Medical Society, the Medical Society of the State of Pennsylvania, the American Medical Association, the American Climatological and Clinical Association, the Medical Club of Philadelphia and the Medical Club of Bethlehem He had been a Fellow of the American College of Physicians since 1925, having been sponsored by three men whose names are greatly revered in our organization, the late Judson Daland, Alfred Stengel and Lewellys Barker

As the handicaps of Parkinsonism bore down more and more, Dr Dever was forced to give up the practice of Medicine in 1939 Finally in 1943, he found it necessary to enter the U S Naval Hospital where he died

His death brought to an end the career of a kindly and scholarly gentleman, who brought to the practice of Medicine great dignity

THOMAS M McMILLAN, M D , F A C P ,

Acting Governor for Eastern Pennsylvania

## DR LOGAN CLENDENING

Dr Logan Clendening, F A C P , Kansas City, Mo , died January 31, 1945, at his home in Kansas City Dr Clendening was born at Kansas City, Mo , May 25, 1884 He pursued pre-medical study at the University of Michigan and received his medical training at the University of Kansas School of Medicine, M D , 1907 Thereafter, he took postgraduate work at Harvard University, University of Edinburgh, Scotland, and the University of Vienna, Austria During the first World War, he served as Major in the Medical Corps of the United States Army

Dr Clendening had been Professor of Clinical Medicine at the University of Kansas School of Medicine since 1928 He was the author of many published articles on medicine and of two textbooks, "Modern Methods of Treatment" and the "Human Body " He was most widely known for his syndicated articles on popular health subjects

## DR FRANK DEVORE GORHAM

Dr Frank DeVore Gorham, F A C P , St Louis, died at the Barnes Hospital, November 27, 1944, of carcinoma of the sigmoid, aged 56

Dr Gorham was born at Cloverdale, Ind , in 1888, A B , 1910, Indiana University, M D , 1912, Washington University School of Medicine, St Louis He served during World War I as captain, M A C , in charge of the Medical Division, Base Hospital 84, France

For many years Dr. Gorham was Instructor in Medicine at Washington University School of Medicine, and a member of the visiting staff of Barnes, St. Luke's and Bethesda General Hospitals. During his earlier career, he had done postgraduate work in Germany, at the New York Post-Graduate Medical School and at the Lenox Hill Hospital, New York. He had published a number of papers, he was a member of the St. Louis Medical Society, Missouri State Medical Society, American Gastro-enterological Association and the American Therapeutic Society, he was a Diplomate of the American Board of Internal Medicine, he was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1927.

# ANNALS OF INTERNAL MEDICINE

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## THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN<sup>1</sup>

By JAMES E. PAULLIN, M.D., F.A.C.P., and CHRISTOPHER JOHN  
McLOUGHLIN, M.D., *Atlanta, Georgia*

THE results of treatment of subacute bacterial endocarditis have been as disappointing and unavailing as of any disease known to medicine. The disease is not uncommon and is found most frequently in localities where rheumatic heart disease is common. Until the present time treatment has been discouraging, attempts to immunize the patient by vaccines, serums, and non-specific shock therapies were very disappointing, in fact these methods seemed to shorten the patient's life rather than prolong it. Intravenous injections of mercurochrome, acriflavine, and gentian violet produced no results, although some of them were encouraging, particularly the use of merthiolate which seemed to cure a similar disease produced experimentally in animals but proved to be of no value in treating human beings.

The advent of the sulfa drugs raised high hopes that at last a remedy had been found which would cure this dread disease. However, sulfanilamide early proved disappointing and other sulfa compounds were tried, then sulfa drugs in combination with other therapeutic measures, such as fever therapy, heparin, and typhoid vaccines. It was then that reports began to appear concerning patients who had recovered from subacute bacterial endocarditis through medical treatment. The advent of penicillin once more raised our hopes but mindful of the disappointments shown by the sulfa compounds we were skeptical of reported cures of subacute bacterial endocarditis by penicillin.

We wish to report six cases of subacute bacterial endocarditis treated with penicillin, in three of which the progress made by the patient has been such that a claim of cure seems justified. It is probable that more cases will be reported as cured by penicillin since the supply of this drug has been greatly increased. It is also probable that most patients will have had an

<sup>1</sup>Received for publication January 29, 1945.

From the Medical Department of the Emory University Medical College.

abortive attempt at cure with some of the sulfa drugs before receiving penicillin. Consequently it is only fair to evaluate the percentage of individuals who may be expected to recover from this disease spontaneously or from the use of other chemotherapeutic agents. In a series of 1,500 cases of subacute bacterial endocarditis Libman<sup>1</sup> reported only 22 spontaneous recoveries. Small as this number of cures is, it is far greater than the three spontaneous recoveries among 1,096 cases collected by Lichtman.<sup>2</sup> Combining these two figures gives a total of 25 spontaneous recoveries among nearly 2,600 cases, or less than 1 per cent. The results of treating subacute bacterial endocarditis by chemotherapy (sulfonamides) offer some improvement over the above figure. Lichtman collected 489 cases to which may be added some reported more recently by Galbreath and Hull<sup>3</sup> and also a few reported by Bunn,<sup>4</sup> which brings the total up to 535. Twenty-four of this number were reported cured, thus giving a total of 4.5 per cent of cases cured by sulfonamides alone and not in combination with other therapeutic measures. The use of sulfonamides in combination with heparin was advocated in the hope that the heparin would prevent the formation of fibrin clots on the valve leaflets and so eliminate the bacterial-laden vegetation from the valves. Of 109 cases reported treated by the combination of heparin and sulfonamides seven recovered, thus showing a total of 6.5 per cent cured. Krusen<sup>5</sup> and others reported that the blood stream can be sterilized by use of hyperpyrexia alone, even though it cannot be kept sterile. The fact that positive cultures from the blood stream can be made within a few days after sterilization of the blood by hyperpyrexia is probably due to the breaking off of infected vegetations from the valves and reinfection of the blood stream. Chemotherapy, in combination with hyperpyrexia induced by the fever cabinet or the Kettering hypertherm, in 61 cases yielded only four cures, or a total of 6.5 per cent. This is almost the same percentage as by chemotherapy alone. Solomon<sup>6</sup> reported 22 cases treated by chemotherapy plus the use of intravenous typhoid vaccine with five cures from *Streptococcus viridans* infection, but 23 other cases reported by Lichtman resulted in only two additional cures. These reports give this form of therapy an average of 15 per cent in the 45 cases reported. Just how much the percentage of cures will increase through the use of penicillin is difficult to determine at this time. It is hoped that the percentage will mount considerably. Herrell, Nichols and Heilman,<sup>7</sup> at the Mayo Clinic, reported that four cases of subacute bacterial endocarditis they had treated with penicillin resulted in failure. However, they used penicillin in very small amounts and what the outcome would have been if they had used larger doses is conjecturable. Evans<sup>8</sup> treated four cases with a cure in one. He found that very large doses were necessary and used four and one-half million units on the individual who recovered. This man is now well and working 10 months after his illness.

The first three cases presented here are frank failures. Two of these cases received less than 3 million units, which from our observation seems

insufficient to produce a lasting cure. On the other hand two of these three were advanced in age, the other, although young, was almost in extremis on admission to the hospital. Failure was expected in one case because the organism isolated from her blood was only slightly inhibited in vitro by penicillin.

#### CASE REPORTS

*Case 1* O D, white female, age 68, was admitted to the hospital July 24, 1944, with the history of illness with fever and general malaise of eight weeks' duration. Five weeks previously she developed generalized aching, night sweats with some loss of weight, and also anorexia and nausea. Two weeks previous to admission she had diarrhea with blood and mucus in her stools. She developed shortness of breath at this time. One year previous to admission a doctor had told her she had a "leak" in her heart. Otherwise her cardio-respiratory history was negative.

*Physical Examination* On admission her temperature was  $100\frac{3}{5}^{\circ}$ , pulse 88, respirations 18, blood pressure 140 mm Hg systolic and 74 mm diastolic. She did not appear acutely ill. The general examination was essentially negative. Heart was enlarged and the rate was regular. She had a grade 3, fairly harsh systolic murmur at the apex and over the aortic area. The spleen was not palpable. No petechiae were observed.

*Laboratory Reports* Red blood cells averaged about 4,200,000, hemoglobin about 11 grams, sedimentation rate varied from 117 mm on admission to 107 mm two weeks later, white blood cells varied from 9,000 to 11,000 and as low as 7,000. Five blood cultures were positive for alpha hemolytic streptococcus, or *Streptococcus viridans*. At 4 p.m. on August 2, her tenth hospital day, she was started on twenty-five thousand units of penicillin in 2 c.c. of saline intramuscularly every two hours.

*Treatment* Before penicillin was started the temperature varied from  $101^{\circ}$  to  $102^{\circ}$  F, and after that it dropped to  $99\frac{5}{10}^{\circ}$ . On the fourteenth hospital day the heart murmur was still the same and the temperature remained about  $99^{\circ}$  F. She was given 400 c.c. of whole blood. She received a total of 2,975,000 units of penicillin up until August 12, 1944. Her temperature remained about  $99^{\circ}$  with the exception of one day from the time the drug was started. She was dismissed from the hospital on August 19. On September 5 she reported that she was not well and was complaining that she ached all over and that her ankles were swelling. Failure in this case was expected because her organisms were only slightly inhibited by penicillin in vitro.

*Case 2* J H, colored male, age 72, was admitted to the hospital on May 16, 1944. He had been in good health until the first of April, 1944, at which time he began to have fever without chills, loss of weight, anorexia, and severe lassitude. His illness forced him to stay in bed for about one week before his admission. At this time he developed a severe precordial pain which was noted only on motion of the chest wall. This was described as a "catch-like" pain. There was no history of previous heart disease, syphilis, or rheumatic fever.

*Physical Examination* The temperature on admission was  $100^{\circ}$  F. Pulse 90. Blood pressure 150 mm Hg systolic and 100 mm diastolic. He was an elderly colored man in no acute distress, but chronically ill. Eyes showed pale conjunctivae with petechiae in the lower left lid. The fundi showed no hemorrhages or exudates but there was one plus arteriosclerosis. The heart was enlarged to the left and there was a to and fro murmur heard over the aortic area. At the apex there was a soft diastolic murmur. The rate and rhythm were regular. The liver was palpable 3 cm below the costal border. There was a right indirect inguinal hernia extending down into the right scrotum. Otherwise physical examination was negative.

*Laboratory Reports* Red blood cell count was 3,800,000 with 10 grams of hemoglobin. Sedimentation rate 85 mm. White blood cells, 10,950, with 83 per cent polymorphonuclears. Blood culture on admission showed an alpha hemolytic streptococcus. Phenolsulfonphthalein test was within normal limits. Non-protein-nitrogen four days after admission was 32, with a total protein of 5.5 grams.

Roentgen-ray showed marked left ventricular enlargement with tortuosity of the thoracic aorta.

*Hospitalization* Cultures of the blood were taken daily after admission, all of which grew alpha hemolytic streptococcus. This was continued until penicillin could be started on May 24. Twenty-five thousand units were given every three hours. On May 29 the cultures of the blood became negative. By this time the patient had already regained his strength and continued to feel subjectively well the remainder of his hospital stay. On June 6 the course of penicillin was completed and 2,800,000 units had been given. The cultures of the blood had remained negative up until June 5 but one done on June 8 was again positive and they remained positive until he left the hospital. On June 13 he was placed on full dosages of sulfadiazine. The blood cultures remained positive and the patient subjectively well. On June 17 he was discharged at his own insistence. When last seen his health and strength were failing rapidly.

*Case 3* C. R., white, female, age 20, was admitted to the hospital on April 17, 1944. At that time she complained of heart and joint pains which began in November 1943 following an attack of influenza with malaise, chills and headache, and paralysis of the left side. In January 1944 she developed a polyarticular migrating pain at the left ankle, with swollen, hot, tender joints involving the ankle and then both knees, wrist, elbow. This cleared up with no residual damage. Two weeks before admission she had an attack of palpitation lasting five to ten minutes. Frequently in the past she had attacks of dyspnea which had been relieved by erect posture. History revealed that she had frequent epistaxis as a child, with sore throat. There is no other history of rheumatism or chorea.

*Physical Examination* Temperature on admission 100.2° F., pulse 120, respirations 40, blood pressure 110 mm Hg systolic and 50 mm diastolic. She was acutely ill, considerably undernourished, with evidence of recent weight loss. The left wrist, hand, fingers, elbow and ankle were swollen, tender, and very painful on motion. The eyes showed some petechiae in the right conjunctiva, fundi were negative. The throat was inflamed. Examination of the heart revealed a diffuse apex impulse with a systolic thrill at the apex and a loud harsh systolic murmur and a low-pitched diastolic murmur heard at the apex. The tip of the spleen could barely be felt. There was some clubbing of the fingers. Reflexes were all hyperactive. She was hyper-irritable and unstable emotionally, crying during the entire time the history was being taken.

*Laboratory Reports* Her red blood cells were 3,900,000, with 12.4 grams of hemoglobin. Sedimentation rate was 115 mm and ranged down to as low as 16 mm an hour before her death. The red cell count did not change markedly. The white blood cell count on admission was 12,000, eighty per cent of which were polymorphonuclears, this ranged as high as 23,000 and as low as 9,300 before her death. Non-protein-nitrogen was 38 mg one month after admission to the hospital and 92 mg before death. Four consecutive blood cultures on admission revealed alpha hemolytic streptococcus. Roentgenogram of the chest taken shortly after admission revealed generalized cardiac enlargement, mitral configuration, and pulmonary congestion.

*Hospitalization* The first five days in the hospital her temperature was spiking, going as high as 104° F. She was started on sulfadiazine on the fourth day and this was continued to the seventh hospital day. Penicillin was started in doses of 200,000

units per day on the eleventh hospital day and this was continued for 20 days. A total of 45 million units were used. The patient went into marked congestive failure during the treatment. She was digitalized and was given ammonium chloride, salyrgan, urea crystals, and vitamins, etc., with little relief. Both pleural cavities were tapped, and 1,000 to 2,000 cc of fluid were removed at various and irregular intervals. Her temperature came back to normal about five days after the discontinuance of penicillin and remained normal throughout the rest of her hospitalization. She became very irritable, would not eat and would not take any medication by mouth. Plasma and all other measures for diuresis and increasing the strength of the heart were unsuccessful. She gradually became weaker and died on the fifty-ninth hospital day.

*Necropsy* was obtained. The diagnoses were (1) Rheumatic heart disease, with mitral insufficiency (2) Subacute bacterial endocarditis, due to alpha hemolytic streptococci (3) Old cerebral embolism.

The first case presents a fairly typical picture of an endocarditis superimposed upon valves of the heart that were already damaged. The failure of penicillin to inhibit organisms isolated from her blood stream made it fairly certain that its use would not be very advantageous. The method of testing for susceptibility to penicillin is simple and requires comparatively few hours. It gives a reasonably accurate indication of what effect the penicillin may have on the organisms *in vivo*. It has been found to be of little value *in vivo* when its use *in vitro* has shown very little inhibition of culture growth. The second case revealed no evidence of valvular damage other than that due to arteriosclerosis. Although his cultures were still positive on dismissal he was subjectively much improved, but soon began to lose ground rapidly. The third case is that of a young woman with a history of epistaxis, sore throats and joint pains, which account for her valvular damage.

The next three cases are of those fortunate individuals who, both subjectively and clinically, have recovered from subacute bacterial endocarditis. Three recoveries out of six cases place this number far above the average for either spontaneous recovery or cure through the use of the sulfa-compounds. These patients did receive some of the sulfa drugs. However, their cultures remained positive while it was being administered. In each of these cases tests were made *in vitro* to determine the susceptibility of the organism to penicillin. In each case it was found to be susceptible to weak solutions of the drug, and thus gave hope it would be effective *in vivo*.

*Case 4* J. M., white, male, aged 16 years, developed rheumatic arthritis at five years of age and since then had recurrent pain in the joints, with fever, palpitation, epistaxis and frequent colds. He was admitted to the hospital in December 1937, with joint involvement, but at that time had no cardiac damage. Tonsillectomy was done in 1938. The diagnosis of myocarditis was made in June 1939. A faint diastolic apical murmur was heard in August 1940 when he had another attack of arthritis. In January 1942 a diagnosis of aortic insufficiency and mitral stenosis was made. In February 1943 he had another attack of arthritis. About June 8, 1944, he noticed pain in his left lower chest. A diagnosis of pneumonia was made and he was started on sulfathiazole. He recovered from this attack in eight or nine days. On June 17, 1944, he had a slight nose bleed. On June 19 he was admitted to the hospital com-



plaining of weakness and a tired feeling for the preceding two or three weeks. He also had some mild exertional dyspnea but no orthopnea or nocturnal dyspnea.

**Examination** Physical examination showed him to be poorly nourished, with a temperature of 101° F, pulse 122, respirations 20, blood pressure 120 mm Hg systolic and 30 mm diastolic. He looked much younger than his stated 16 years. The eyes were essentially negative. The chest showed a rather marked Harrison's groove and a rachitic rosary. The heart was enlarged and there was a harsh, high pitched, short systolic murmur heard all over the precordium, best at the apex, and a harsh, high pitched, diastolic murmur in the aortic area, which could also be heard at the apex. The pulmonic second sound was loud and snapping. There was a Corrigan pulse with pulsating capillaries and pistol shot femorals. The liver could be demonstrated by percussion 3 cm beneath the costal border but it could not be felt. The spleen was barely palpable.

**Laboratory Reports** On admission, on June 19, the red blood cells were 3,180,000, hemoglobin 9 grams, sedimentation rate 33 mm. On June 23 the sedimentation rate had jumped to 138 mm. The white cell count varied from 10,000 to 18,000.

**Roentgenogram** showed the heart to be enlarged to the right and the left atrium showed very marked dilatation, displacing the esophagus to the right and posteriorly. Blood cultures taken on June 19 and June 21 showed a positive growth of *Streptococcus viridans* which was sensitive to penicillin. For the first 10 days of hospitalization he ran a spiking fever which averaged about 102° F at its peak but one day went as high as 104°.

**Treatment** Penicillin was started on June 28 and he received 25,000 units intramuscularly in 2 cc of normal saline every two hours. On the third day of treatment the temperature dropped to normal and remained there for the duration of his hospitalization. He received a total of 4 million units of penicillin and was dismissed from the hospital on July 24, 1944. Additional blood cultures, two of which were taken during August, showed no growth. He was dismissed on 1 gram of sulfadiazine daily "for life." His last visit was August 25, 1944, at which time he was symptom free. His red blood cells then numbered 3,880,000, white blood cells 7,900, hemoglobin 11.5 grams.

**Case 5** L. H., colored female, 20 years of age, was admitted to the hospital on February 10, 1944. At the age of six this patient had rheumatic fever with arthritis so severe that she used crutches for six months. In 1941 an aortic diastolic murmur was found and a diagnosis made of rheumatic heart disease with aortic insufficiency. Kahn tests in 1940 and 1941 were positive. In 1941 a lumbar puncture yielded negative spinal fluid. The day before admission to the hospital she complained of mild headache which lasted all evening. She also had some slight fever and pain in the knees when walking.

**Physical Examination** Her temperature on admission was 103° F, pulse 120, respirations 22, and blood pressure 120 mm Hg systolic and 60 mm diastolic. She was not acutely ill and was moderately well nourished. There were no petechiae. No joints were involved except that the knees were somewhat painful on passive movement. The glands in the posterior cervical and axillary regions were palpable but not tender. The eyes showed some pulsating vessels in the fundi. The left border of dullness of the heart was 9 cm to the left. A grade 2 systolic murmur was heard at the apex, transmitted to the axilla. There was a slight diastolic murmur heard at the secondary aortic area but none at the apex.

**Laboratory Reports** Sedimentation rate was 51 mm, white blood cells numbered 10,750, with 86 per cent polymorphonuclears. Kahn reaction was negative. The first blood culture yielded 165 colonies per cc of alpha hemolytic streptococcus. Fluoroscopic examination of the chest was indicative of rheumatic heart disease with mitral involvement. There was no suggestion of congestion or pleural fluid. Spinal fluid examination was negative. The electrocardiogram showed no significant findings.

*Treatment* was symptomatic for the first three days and patient was placed on sulfadiazine. Two days later the fever curve returned to normal and then rose to 99° F and then to 102° and 103°, with strongly positive blood cultures. On the twelfth hospital day penicillin, 250,000 units a day intramuscularly, was started with individual doses every two hours day and night for 14 days. The day after this therapy was started the temperature returned to normal and until therapy was stopped on the twenty-sixth hospital day did not rise significantly. From the twenty-sixth to the thirty-second hospital day the temperature curve ran between normal and 100° F and then came down to normal and stayed there. The patient felt greatly improved after therapy was stopped and gained in weight and strength. The day before therapy was begun there were 27 colonies of alpha hemolytic streptococcus per c c of blood and the day after therapy was started the organisms had completely disappeared. She was discharged from the hospital on March 21, 1944. On March 28, and again on April 11 blood cultures were still negative. Sedimentation rate also came down to 40 mm in one hour on discharge, 34 mm a week later, and 31 mm two weeks thereafter. The white cell count was normal during the entire course of penicillin, it became slightly elevated when the penicillin was stopped and then fell to normal with the fever curve. During her course in the hospital she received two transfusions of 500 c c each, and also ferrous sulfate by mouth. Her red cell count was 5,000,000, hemoglobin 12 grams. When seen three weeks after discharge she was asymptomatic, feeling well and quite strong and ready to return to work. Six months later she was still well and symptom free and working daily without difficulty.

*Case 6* T A S, white male, age 64, was admitted to the hospital on January 1, 1944, complaining of weakness of two months' duration. In July 1943 he had been told that he needed several abscessed teeth removed, and his local physician said his physical condition was satisfactory. Between July and October 19, one-third of his teeth were extracted, one or two at a time. Late in October he lost his appetite and energy, and was no longer able to work as long or as hard as usual. He had no pain at this time. Between October and December he had frequent night sweats. He had no chills or fever. These symptoms gradually progressed until December when he was confined to bed because of weakness. There was no dyspnea. His weight loss was approximately 30 pounds, decreasing from 150 pounds to 120 pounds.

*Past History* He had an unknown fever of some sort when he was quite young. No other serious illnesses.

*Physical Examination* He was a poorly nourished white male. There was a small petechial hemorrhage on the palpebral conjunctiva of the right lower eye lid. The heart was not enlarged to percussion. There was a distinct, soft, blowing systolic murmur heard over almost the entire precordium. The second sound was slightly accentuated but there were no murmurs. Blood pressure was 110 mm Hg systolic and 70 mm diastolic. Liver and spleen were not palpable.

*Laboratory Reports* Urinalysis frequently showed a heavy trace of albumin and usually from 1 to 3 red blood cells per high power field. Red blood cell count on admission was 3,300,000, white blood cells 10,000, hemoglobin 10.7 grams. On January 12 his white cell count had risen to 21,350, but by February 2 had dropped again to 12,000. On February 15 it came down to less than 9,000 and remained there throughout his stay. Sedimentation rate on admission was 77 mm, rising as high as 104 mm on January 12, 1944, dropping again to 100 mm on February 2, 1944, and decreasing gradually to 60 mm at dismissal. Between January 5 and January 11 four cultures were positive for *Streptococcus viridans*. On January 18 a culture showed inhibition of growth over half of the Petri dish with penicillin diluted 1:250 units per c c and 1 c c placed in a dish. A culture on January 22 showed six colonies. On January 24 the culture showed two colonies, on January 29 two colonies and from then on all cultures were negative, although they were taken

regularly at frequent intervals and eight were made. Electrocardiogram showed no definite evidence of myocardial damage. Neo-prontosil (intramuscularly) was started on the sixth day of hospitalization and was continued in what was considered adequate dosage until the administration of penicillin was begun. From the time of his admission on January 1 until the time penicillin was started on January 29 he had a spiking temperature averaging  $102^{\circ}$  F but at times did become elevated to  $103^{\circ}$ . On January 29 he was started on penicillin and from then on his temperature stayed below  $100^{\circ}$  until the very day that the penicillin was stopped on February 12, and on that day he ran a temperature of  $103^{\circ}$  at 8 o'clock in the morning for some unknown reason. His temperature dropped then and remained between  $98^{\circ}$  and  $99^{\circ}$  for the duration of his hospital stay. He was dismissed from the hospital on March 6, 1944. At that time he weighed 131 pounds and had received a total of 4,225,000 units of penicillin.

*Progress Notes* On January 9 several small petechiae were discovered in the left anterior chest wall. On January 14 there were two fresh hemorrhages in the right fundus, one medial and one lateral to the disc. There was a similar hemorrhage in the left eye superior to the disc. On the ninth he also developed an Osler's node at the tip of the left forefinger which was painful and tender. This disappeared within five days. On January 24 he had developed some petechiae in the left conjunctival sac and the hemorrhages in the eyes had resolved. On January 25 his condition became much worse, his speech was irrational and indistinct and he appeared disoriented, and had an aphasia. The cranial nerves were apparently intact, all the abdominal reflexes and cremasteric reflexes were absent. The pupils reacted rather sluggishly to light. At this time it was considered that he might have had an embolus from a vegetation to the left mid-cerebral artery. The following day he was better oriented and appeared to have partially recovered. On February 3 no marked changes were observed and the sedimentation rate was even more elevated than previously but the patient felt that his appetite was better.

*Follow-Up* On March 22 his weight had increased to 148 pounds. His appetite was good. He had no fever and no complaints. The left border of cardiac dullness was 10 cm from the midsternal line in the fifth left interspace. There was a rather loud systolic murmur but no diastolic murmur was heard. Blood pressure was 140 mm Hg systolic and 76 mm diastolic. Red blood cells numbered 3,830,000, white blood cells, 12,600, hemoglobin 12.2 grams. Sedimentation rate was 42.5 mm in one hour. On April 19 he weighed 152½ pounds. December 25 he is quite well.

All of the above cases show evidence of earlier damage to the valves of the heart before the onset of the endocarditis. Cases 4 and 5 showed a long history of valvular damage of considerable extent, yet they were able to withstand the onslaught of bacterial invasion and to recover without much appreciable additional damage to the valves. Case 6 in particular presented a gamut of clinical manifestations varying from the slight fever, weakness and weight loss which accompanied the onset of the disease, down through progressive wasting away and loss of orientation through a cerebral accident and up again from the shadows to new life and health. One of the striking factors in these cases is the unusually large amount of penicillin required to produce a cure in these patients. Evans<sup>8</sup> found that it required 4,500,000 units to effect a cure in his patient. We too have found that far above the usual amounts of penicillin must be used. Two hundred to three hundred thousand units daily must be injected regularly every two hours, day and night until about four million units have been given. Herrell et al<sup>7</sup> used a

continuous intravenous drip method to administer a total of 80,000 units daily. The use of continuous intravenous drip probably has the advantage of giving the patient a more uniform and constant concentration of penicillin in the blood, which is very desirable, than by the intramuscular injection every two hours. However, the difficulty of holding an arm quiet for the many days necessary to administer the treatment makes it appear easier on the patient if the intramuscular method is used.

The first two cases in our series received less than three million units of penicillin and the others received approximately four million or more units. This is far above the average doses required for the successful treatment of other conditions which respond to penicillin. Moreover, it must be continued in concentrated doses for a longer period of time than is necessary in the treatment of other penicillin-susceptible infections. None of the patients treated in this series suffered any reactions which could be attributed to the penicillin. Very few serious reactions have been reported during its use. Herrell<sup>7</sup> states that it can be used with safety even in severe anemia, leukopenia or even complete agranulocytosis. With the improved purity of penicillin even fewer reactions are likely to occur.

#### SUMMARY

We have presented six cases of subacute bacterial endocarditis proved by repeatedly positive blood cultures in each case. Three of these cases were rather hopeless from the onset, the other three, although they appeared to be hopeless, nevertheless responded so well to penicillin therapy that they are still alive and well and without subjective or objective evidence of a bacterial endocarditis. The two adults are again working daily at their respective occupations and have gained in weight and strength. It is now six months since the dismissal of one from the hospital, and nine months or more for the other two patients. They will be followed carefully for some time to come.

It is felt that failure in some cases which have been reported in various journals may have resulted from insufficient concentration of penicillin, or an inadequate total dosage. All cases seem to require at least 4,000,000 units and now that it is more readily available commercially there should be no reason why even greater total dosage could not be used.

These three cures out of six cases are but a small number, and no accurate percentage of cures can be derived from this small series. However, it does show that in patients whose organisms are known to be susceptible to penicillin there can be cure even in such serious illnesses as subacute bacterial endocarditis. We know that the results of cure with penicillin will rise far above the 1 per cent of cases that recover spontaneously and we hope that it will also give a much greater percentage of cures than the 4.5 per cent to 15 per cent of cures obtainable with various combinations of sulfa drugs.

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# INHALATION OF PENICILLIN AEROSOL IN PATIENTS WITH BRONCHIAL ASTHMA, CHRONIC BRONCHITIS, BRONCHIECTASIS AND LUNG ABSCESS PRELIMINARY REPORT\*

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THE purpose of this communication is to present the results of an exploratory study on the technic, safety and clinical effectiveness of inhaling penicillin aerosol in patients with bronchopulmonary infection. Many questions concerning dosage of the drug, length of treatment and choice of apparatus require further investigation. Our preliminary findings are reported in order that other workers in this field may study this relatively simple method of local application of penicillin to the bronchi and lung parenchyma, since the response in some patients has been of an encouraging nature. That penicillin aerosol penetrates the lungs and may be recovered from the urine in rabbits and normal human beings was demonstrated by Bryson, et al.<sup>1</sup>

## HISTORICAL

The administration of drugs by inhalation through the lungs has been employed for many years in patients with asthma and pulmonary emphysema. When a suspension of a substance is produced by the passage of air or oxygen through a nebulizer, the resulting mist is termed a "nebulin" or an "aerosol." It has long been known that particulate substances of small size penetrate the alveoli, and that the size of the particles is dependent upon the nature of the nebulizer used. The beneficial results of inhaling the nebulized solution of 1:1000 epinephrine in patients with asthma were reported some years ago by Heubner<sup>2</sup> and Lageder.<sup>3</sup> An important practical advance in this therapy was made by Graeser and Rowe,<sup>4</sup> who suggested the more concentrated 1:100 solution of epinephrine, employed in a hand bulb nebulizer that provided a fine suspension of the drug. In simplicity of technic, rapidity of action and relative freedom from constitutional side effects, this method of administration presented practical administration over injection of epinephrine by hypodermic. The use of 1

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per cent epinephrine and 1 per cent neosynephrine by continuous inhalation was studied by Richards, Barach and Cromwell<sup>5</sup> in patients with bronchial asthma and other clinical entities with bronchial constriction. The use of these substances has been found to be of clinical value not only in cases of bronchial asthma and pulmonary emphysema,<sup>6</sup> but also in pneumonia and pulmonary edema<sup>7,8</sup> and in irritant gas poisoning<sup>9,10</sup>. A more stable and less irritating suspension of epinephrine is obtained if a 5 to 20 per cent solution of glycerin is added, as shown by the classical study of Abramson,<sup>11</sup> but the concentrations of penicillin used in this investigation are high enough not to require addition of glycerin. Lockey<sup>20</sup> also found that the addition of 5 per cent glycerin to a 1 per cent epinephrine solution resulted in less irritation and dryness of the throat.

The employment of chemotherapeutic agents as aerosols had the theoretical advantage of a high local concentration with a relatively low blood level of the drug, since nebulized solutions penetrate to the depths of the lungs.<sup>2</sup> Castex, Capdehourat and Pedace demonstrated that a 5 per cent solution of sulfanilamide resulted in clinical improvement in cases of bronchopulmonary suppuration<sup>12,13</sup>. Krueger, et al<sup>14</sup> showed that the material was uniformly distributed through the alveoli of the lungs by employing India ink in monkeys and mice. Chambers et al<sup>15</sup> developed a method of preparing minute microcrystals of sulfathiazole which were sprayed into the lungs by an atomizer supplied with compressed air. They demonstrated that significant amounts of sulfathiazole can be absorbed through the lungs with the production of high blood levels of this drug. The inhalation of the nebulized solution of promin was shown to prevent the development of experimental tuberculosis in guinea pigs by Barach et al<sup>16</sup>. Promin solution has recently been used as an aerosol in patients with pulmonary tuberculosis by Edlin et al<sup>17</sup>. Stacey<sup>18</sup> reported marked improvement after inhalation of nebulized sulfathiazole solutions in patients with bronchiectasis.

The use of penicillin as an aerosol was suggested by Bryson, Sansome and Laskin<sup>1</sup>. Since penicillin is known to be bacteriostatic in extremely high dilutions, inhibiting the growth of hemolytic streptococci in quantities as low as 0.01 microgram per c.c., the potential value of inhaling a penicillin aerosol was considered likely. The efficacy of local instillation of penicillin solution in patients with empyema due to pneumococcus infection indicated that this drug was active in the presence of blood and pus. Penicillin is not inactivated by the presence of para-amino-benzoic acid in purulent exudates, in contrast to the sulfonamides<sup>19</sup>. Bryson et al<sup>1</sup> showed that penicillin aerosols could be recovered from the lungs of rabbits. With a rebreathing bag oxygen mask nebulizer apparatus 3.2 per cent of 25,000 units of penicillin aerosolized in the mask were recovered in the urine during the first 12 hours after inhalation, but when a human subject inhaled the penicillin for 15 seconds and held his breath or 15 seconds thereafter these authors found that 60 per cent of the aerosolized penicillin was recovered in the urine dur-

ing a 12 hour period, which compared favorably with an average recovery of 60 per cent after intravenous injection. It is evident, however, that patients suffering from bronchial and pulmonary disease would not generally be able to hold their breath for a prolonged period of time.

In this communication various clinical methods of inhaling penicillin aerosol were tried. The initial results obtained in a series of patients with bronchial asthma complicated with bronchial infection, bronchiectasis, lung abscess and pulmonary emphysema with fibrosis will be presented.

The consideration of the optimal duration of treatment was subordinated to the primary purpose of determining the safety and early response to this chemotherapeutic approach in 20 patients, since the supply of the drug was limited. A small number of experiments on animals was performed to determine the possible irritating effect on the bronchi and lung parenchyma and the protective value of penicillin aerosol in systemic infection.

### METHODS

In the routine use of nebulized solutions of epinephrine and neosynephrine the end of the nebulizer is held within the partly opened mouth and the patient inhales the aerosol as it is continuously produced by a stream of 5 liters per minute of oxygen passing through the nebulizer. During the expiratory cycle the nebula of the drug passes into the outside air. In order to overcome an undue loss of penicillin aerosol an oxygen mask nebulizer apparatus was first employed in which the open end of the nebulizer was inserted through the mask between the lips of the patient. The aerosol of penicillin was then inhaled during inspiration and the aerosol remaining in the exhaled air was delivered into a rebreathing bag. A considerable portion of the drug condensed in the rebreathing bag which could not be easily re-used. Therefore, an enlarged glass nebulizer was substituted for the mask to collect penicillin in the exhaled air for rebreathing.

The volume and shape of the nebulizer were ultimately changed by fusing a 1000 cc glass bulb to the upper surface of the nebulizer. The glass tube from the nebulizer was lengthened and inclined upwards. The purpose of this modification was to collect within the enlarged nebulizer that part of the penicillin aerosol that remained in the expired air and to prevent excessive condensation on the inner surface of the glass bulb. The nebulizer\* employed produced a suspension in which the majority of the particles were smaller than 1 micron.

In order to produce penicillin aerosol only during the inspiratory cycle a glass or metal Y tube was inserted in the rubber tubing between the oxygen regulator and the nebulizer. In operation, the open end of the Y tube is covered by the thumb of the patient (or nurse) before the start of inspiration and released before the end of inspiration. If ordinary respiration is adopted, the particles of penicillin are apt to be in contact with the bronchial

\* The nebulizer is made by the Vaponefrin Co., Upper Darby, Pa.



surface for a longer period of time than if deep inhalations and breath-holding are employed. However, under the latter conditions higher blood levels are obtained, since the drug is then absorbed from the expanded alveolar surface. When the local deposition of the drug on the bronchial wall is sought, the blood level may be of secondary importance. On the other hand, in lung abscess deep breathing may result in better penetration of the cavity if the bronchi are enlarged by expansion of the chest. The size of the particles is another factor that merits consideration. The larger particles settle on the upper air passages and the smallest sized ones penetrate to the alveoli. The nebulizer that produced a majority of particles under one micron was selected in this study. The flow of oxygen is now generally set at 8 liters per minute. This may vary between 4 and 10 liters per minute depending upon the length of time which is considered optimal for nebulization of the penicillin solution. The mouth is closed about the end of the nebulizer which is inserted over the tongue for about two inches. The carburator (or extra orifice in the nebulizer) is left open.

The development and trial of modifications of apparatus for inhalation of penicillin aerosol are proceeding. An automatic production of penicillin aerosol only during the inspiratory cycle is accomplished by a specially constructed demand valve apparatus which does not require the cooperation of the patient.<sup>21</sup> The small size (ordinary) nebulizer may also be employed, provided it is of the type that produces particles that are mostly under 1 micron in diameter, such as the Vaponefrin or the DeVilbiss No. 40 nebulizer. The nebulizer with an added 1000 c.c. volume makes possible the reinhalation of some of the aerosol in the patient's expired air together with that nebulized during inspiration. The attachment of the glass one liter bulb is so arranged as to prevent the aerosol formed during inspiration from entering this chamber, and in that way wasteful condensation of the drug is avoided.

The concentration of penicillin employed varied between 2,000 and 100,000 units dissolved in 1 c.c. of physiological saline. A concentration of 20,000 units per c.c. was employed in the early part of this investigation. More recently, dilutions of 40,000 to 50,000 units per c.c. were used. The solution is made by inserting 2 c.c. of 0.85 per cent saline into the standard bottle containing 100,000 units of penicillin and withdrawing 10 c.c. for each treatment in a sterile tuberculin syringe. In order to avoid waste of the penicillin 0.5 c.c. of normal saline is inserted into the original bottle when it is empty and a dilute solution of the penicillin that clings to the side of the glass is removed and used. An illustration of the apparatus is shown in the accompanying photograph (figure 1).

In infants and small children penicillin was at first administered by a catheter inserted in the oropharynx. Since the larger sized particles will condense in the catheter if it is taken directly from the nebulizer and thereby obstruct the flow of the aerosol, an empty bottle trap was inserted between the nebulizer and the tube that leads to the rubber catheter. A small amount of penicillin solution is condensed in the flask in this way and the remainder

of the nebulin consisting of particles of small size will now penetrate a No 10 or No 12 French catheter

In adults penicillin administered by oropharyngeal insufflation does not result in as high blood levels as are produced by the oral method previously described In infants and small children treated by the catheter method



FIG 1

beneficial clinical results as well as the presence of traces of penicillin in the blood have now been demonstrated Since local deposition on the bronchi may be the chief intention of penicillin aerosol administration, the blood level is not the main factor A mask nebulizer apparatus is now also being used in children \*

\* A separate report of the studies in children will be referred to later

## TAL AND CLINICAL RESULTS

## EXPERIMENT

on of penicillin aerosol when introduced into the  
 The possibility of irritation When small amounts of penicillin  
 lung was subjected to invade of distilled water, coughing was noted It  
 were inhaled in a solution mon of distilled water was irritating both to nor-  
 was then found that inhalatue to its hypotonicity, and that normal saline  
 mal subjects and patients, defective experience of irritation Penicillin was  
 could be inhaled without sub physiological saline In four of 20 patients  
 then uniformly dissolved inue to inhalation of penicillin aerosol presented  
 the possibility of irritation d bronchial asthma, increased cough was noted at  
 itself In one patient with b tion of 200,000 units per day in a concentra-  
 the end of seven days' inhala However, it was difficult to tell whether this  
 tion of 40,000 units per c c osol or whether the patient had acquired an  
 was due to the penicillin aerresult of a cold In some patients coughing is  
 intercurrent infection as the r the physical effect of the solution itself and to  
 produced immediately due to considered an irritant effect since it occurs with  
 deep breathing This is not c In a second patient who had had bronchiec-  
 0.25 per cent neosynephrine s for 16 years there appeared to be a diminut-  
 ation of the peribronchial shad sows at the end of two weeks' inhalation of  
 tion of the peribronchial shad of one month of inhalation of penicillin  
 penicillin aerosol, but at the che bronchi by roentgen-ray appeared to be  
 aerosol the shadows around it also complained at this time of a sensation  
 slightly increased The patient al margin Another patient with bronchiec-  
 of irritation at the upper sternreness at the end of five days' inhalation of  
 tasis experienced substernal sohe same time urticaria on the thigh  
 penicillin aerosol, and noted at an acute lung abscess, felt a slight irritation

A fourth patient, who had f seven days' inhalation of penicillin aerosol  
 under the sternum at the end of a disappearance of a fluid level and only a  
 However, roentgen-ray showed sharply defined cavity at this time In 16  
 vague outline of a previously of seven days to one month, no subjective or  
 other cases treated for periods ation were encountered In 10 normal and  
 objective manifestations of irri on of penicillin between 20,000 and 100,000  
 miscellaneous subjects, inhalat tion of irritation In all the cases that com-  
 units per c c resulted in no sens the sensation disappeared on the following  
 plained of substernal irritation, soreness of the tongue or gums was noted,  
 day In three subjects slight s teeth were said to be shiny, and the tartar  
 and in one of these patients the apparently removed

was made before and after penicillin aerosol  
 Roentgen-ray examination whether improvement occurred, but especially  
 therapy not only to determine wion or edema which might have taken place  
 to detect any signs of inflammat The roentgen-ray of the lungs did not  
 as the result of penicillin aerose except possibly in the case of bronchiectasis  
 reveal any evidence of irritation anges were slight and may not have been due  
 referred to above in which the ch o  
 to the drug

Inhalation of penicillin in aerosol form may perhaps produce transient irritation in the trachea in some instances. The majority of the treated cases (16 of 20) made no complaint of this nature. In the patient with bronchiectasis who was treated for one month with inhalation of 150,000 units daily, 40,000 units per c c, there was no subjective complaint and repeated roentgen-rays showed no sign of an irritant effect of the drug. The possibility that the lung parenchyma is irritated by the aerosol appears to be remote. The larger sized particles in the aerosol are more apt to precipitate in the upper air passages and may account for the sensation of soreness under the sternum that was mentioned in the cases referred to above. However, the symptom was slight and transient. The soreness of the tongue may have come from solution inadvertently spilling into the mouth\*.

The possibility of allergic reaction to the drug must be borne in mind, especially in patients with asthma, although no systemic manifestations of this kind have been observed. In two patients who received penicillin aerosol for three days an urticarial eruption was encountered. However, this disappeared in two days even though penicillin inhalation was carried on for two and six days thereafter.

### ANIMAL EXPERIMENTS

Experiments were performed on rats to ascertain whether penicillin could be absorbed effectively by the inhalation route. White rats, weighing from 150 to 200 gm each, were injected with 0.1 c c of a rat culture of hemolytic streptococcus. One group was kept as controls, a second received penicillin by intramuscular injection and a third group inhaled penicillin aerosol. In the latter group the heads of rats were placed in glass "helmets" into which penicillin aerosol was passed by means of a stream of oxygen flowing continuously through a glass nebulizer containing the penicillin dissolved in normal saline. After the desired amount of penicillin had been nebulized, it was followed by 1 to 2 c c of normal saline in order to salvage the penicillin condensed on the walls of the nebulizer. The flow of oxygen used was 4 liters per minute, and the amount of penicillin administered to each rat varied from 10,000 to 25,000 units.

\* Further observations were made on the possible irritating effect of penicillin. The effect on normal rats of inhalation of sodium penicillin in a concentration of 50,000 units per c c was studied by administering the aerosol in the hood apparatus, 20,000 units daily for five successive days. Four treated animals were compared to four animals to whom a similar volume of normal saline was administered and to four additional untreated control animals. In addition a total of 10 rats, including two controls, were treated by 5 inhalations on successive days of 1 c c neosynephrine, sulfathiazolate, sulmeform, 20 per cent potassium iodide solution, and 25 per cent sulfadiazine in ethanalamine solution. Microscopic section of the lungs of the penicillin treated animals showed no significant differences as compared to the animals receiving saline, the untreated controls, and the miscellaneous group. In each series scattered areas of congestion, edema, atelectasis and occasional hemorrhages were observed. In no instance was there inflammatory change in the bronchi.

In a recent series of patients calcium penicillin has been found to produce superior aerosol than the sodium salt. It is uniformly preferred by patients since it has less odor and it is much less apt to provoke coughing, even in patients who cough after inhalation of sodium penicillin.

With this method of administration much of the drug was lost by condensation on the glass "helmets" and on the animals' fur, as well as by escape from the "helmet" with the stream of oxygen

TABLE I  
Effect of Penicillin by (A) Intramuscular Injection and (B) Inhalation as Aerosol on the Mortality of Rats Infected Intraperitoneally with a Fatal Dose of Hemolytic Streptococcus Culture

	Penicillin Dose in Units	No Rats Used	Mortality		Survival Time in Hours
			No	Per Cent	
Controls	0	31	31	100	27
(A) Intramuscular Injection	10,000	6	1	16.6	89
	15,000	3	0	0	—
	20,000	16	1	6.2	143
	25,000	3	2	66.0	106
Total		28	4	14.4	53
(B) Inhalation of Aerosol	10,000	8	6	75	22
	20,000	16	11	69	62
	25,000	7	2	28.6	103
Total		31	19	61.3	53

Table 1 shows the results of such experiments on a total of 90 rats. Of 31 control animals, all died, the average length of life after injection of 0.1 c.c. hemolytic streptococcus culture being 27 hours. Of 28 rats given penicillin by injection only four (14.4 per cent) died, and these animals lived an average time of 117 hours after infection. In the third group of 31 rats given penicillin by inhalation 19 (61.4 per cent) died, living an average time of 53 hours after infection. It is evident, therefore, that penicillin given by inhalation may protect rats against systemic hemolytic streptococcus infection, but that owing to obvious loss during its administration, the protection is less effective than a comparable dose injected intramuscularly. With larger doses penicillin aerosol is more effective. When 10,000 units of penicillin were administered 75 per cent of the rats died, surviving only 22 hours, while with 25,000 units only 28.6 per cent died, surviving on an average of 115 hours after infection. As indicated above, only 12,500 units were available during the inspiratory cycle of respiration.

The concentration of the penicillin solution used seemed to make little difference in the results. Concentrations varying from 1,000 to 20,000 units per c.c. were used, but no correlation with the mortality rate could be noted in this small series.

In order to determine whether inhalation of penicillin aerosol resulted in pathological changes in the lungs or bronchi a study was made of the lungs of 19 rats that had previously inhaled penicillin aerosol. The total amount of penicillin inhaled varied from 20,000 to 115,000 units per rat, given in

concentrations varying from 2,000 to 40,000 units per cc of solution vaporized. In some cases the inhalations were spread over four or five days, and in others the doses were given in a single inhalation. The rats were usually killed 18 to 20 hours after the last inhalation, but in a few cases were sacrificed immediately following inhalation. They were killed either by a blow on the head, by immersion in an atmosphere of nitrogen, or by injection of an immediately lethal dose of nembutal. Thirteen control rats, receiving no penicillin, were sacrificed similarly.

Microscopic sections of the lungs of the normal rats revealed at times scattered areas of edema and congestion, and occasional patches of atelectasis. The lungs of rats killed by a blow on the head or by nitrogen showed occasional small hemorrhages, possibly caused by the method of sacrifice of the animal.

The penicillin treated lungs showed similar findings, but the edema and congestion appeared somewhat more marked and the atelectatic patches were more frequently noted. As in the control lungs, occasional slight hemorrhages were found in the lungs of those animals killed by a blow on the head or by nitrogen. In one control lung and in two penicillin treated lungs, signs of bronchopneumonia were observed, but these appeared to be of too long duration to be related to the experimental procedure.\*

The differences between penicillin treated and control lungs were, however, very slight, and did not appear to indicate an irritant effect of penicillin. Furthermore, the small and larger bronchi showed no sign of inflammation in either group. It is not yet known whether the slight differences shown were caused by the process of inhaling an aerosol, without any specific action by the penicillin. The control animals were not held in the glass "helmets" and did not inhale normal saline, as is being contemplated in a new series of experiments.

#### EFFECT OF PENICILLIN AEROSOL ON PREDOMINATING ORGANISMS IN THE SPUTUM

The effects of inhalation of penicillin aerosol on the pathogenic organisms recovered from the sputum in 18 tested patients is shown in table 2. It will be seen that in 15 cases the culture of the sputum after penicillin therapy did not show the previously determined organism and in one patient in whom the pretreatment specimen was lost, no pyogenic organisms were found after inhalational therapy. The second culture was taken generally 24 hours after termination of penicillin aerosol treatment. In one instance the organism identified from the sputum was not found to be sensitive to penicillin although in this case there appeared to be a marked regression of the lung abscess by roentgen-ray. In the eight other tested cases the recovered organisms were found to be sensitive to penicillin although not generally as sensitive as the standard organism. In some patients who were treated for

\* Dr. Homer D. Kesten kindly aided in the interpretation of the sections.

one week with inhalation of penicillin aerosol the pathogenic organism re-occurred later, with reappearance of symptoms. Since this communication records in the main the early results of inhalation of penicillin aerosol, the length of time these organisms, found in the sputum prior to treatment, remained absent from the patients' expectoration will be presented in a later report.

### PENICILLIN BLOOD LEVELS DURING AND AFTER INHALATION OF PENICILLIN AEROSOL

The blood level of penicillin was determined at different times during the first hour or more after inhalation of the aerosol in the majority of patients, as shown in table 3. Although the dosage varied in certain patients the blood level as seen in the table represents that which occurred after the dose most generally used in the individual patient. It will be seen that in the largest number of patients blood levels of 0.1 to 0.4 were found during the first 15 minutes to one hour after the inhalation. In two patients a blood level of 1.4 to 1.8 was found one-half hour after inhalation of penicillin.

TABLE II

Effect of Inhalation of Penicillin Aerosol on Organisms Recovered from the Sputum

Case No	Sputum Culture		Sensitivity of Sputum Organism to Penicillin
	Before Treatment	After Treatment	
1	Hemolytic <i>Staph aureus</i>	Unidentified Gram + diplococci	Neither organism sensitive to penicillin
2	<i>Strep viridans</i>	<i>B aerogenes</i>	<i>Strep viridans</i> $\frac{1}{4}$ as sensitive to penicillin as standard organism
2	Pneumococcus, type 31	No pneumococcus <i>B coli</i> predominate	Pneumococcus considered sensitive to penicillin
4	Pneumococcus, type 3	No pneumococcus <i>B aerogenes</i>	Pneumococcus $\frac{3}{4}$ as sensitive to penicillin as standard organism
5	<i>Strep viridans</i>	No <i>Strep viridans</i> <i>B aerogenes</i>	<i>Strep viridans</i> $\frac{1}{2}$ as sensitive to penicillin as standard organism
6	Hemolytic strep L5	No hemolytic strep <i>Strep viridans</i>	Hemolytic strep equal to standard in sensitivity
7	<i>Strep viridans</i>	<i>B aerogenes</i> in pure culture	—
8	Hemolytic strep, B Hemolytic <i>Staph aureus</i>	<i>B proteus</i>	Hemolytic strep $\frac{1}{4}$ as sensitive to penicillin as standard organism
9	Hemolytic and non-hemo strep, <i>Staph aureus</i>	—	—
10	Hemolytic <i>Staph aureus</i> <i>Strep viridans</i>	<i>B aerogenes</i>	—

TABLE II—Continued

Case No	Sputum Culture		Sensitivity of Sputum Organism to Penicillin
	Before Treatment	After Treatment	
11	Gram + diplococcus	<i>B coli</i>	Slightly more sensitive to penicillin than the standard organism
12	Hemolytic <i>Staph aureus</i> <i>Strep viridans</i>	<i>B aerogenes</i>	—
13	<i>Strep viridans</i>	<i>B aerogenes</i>	<i>Strep viridans</i> $\frac{1}{2}$ as sensitive to penicillin as standard organism
14	<i>Strep viridans</i>	<i>B aerogenes</i>	
15	<i>Strep viridans</i> <i>Staph aureus</i> Hemolytic strep	No pneumococcus <i>B coli</i>	Hemolytic strep $\frac{1}{2}$ as sensitive to penicillin as standard organism
16	Hemolytic strep <i>Strep viridans</i> <i>Staph albus</i>	No pneumococcus <i>B aerogenes</i>	<i>Strep viridans</i> $\frac{1}{2}$ as sensitive to penicillin as standard organism
17	<i>Strep viridans</i>	No pneumococcus <i>Strep viridans</i> *	—
18	—	No pneumococcus No staph No strep	—
19	<i>Strep viridans</i>	No pneumococcus <i>B aerogenes</i>	—
20	Hemolytic <i>Staph aureus</i> <i>Strep viridans</i>	No pneumococcus Gram—bacillus predominating	Hemolytic <i>Staph aureus</i> equal in sensitivity to standard organism <i>Strep viridans</i> $\frac{1}{2}$ as sensitive as standard organism

\* Sputum culture taken 7 days after termination of penicillin aerosol therapy

In general, higher levels of penicillin in the blood were obtained after higher dosages, although in cases in which a large amount of purulent expectoration was present and in cases with pulmonary fibrosis, the blood level tended to be lower. Considerable variation may be accounted for on the basis of differences in the breathing pattern of the individual patient. Higher blood levels will be obtained if the patient is instructed to take a deep breath during the inhalation of the aerosol and hold it for several seconds before exhaling. In all instances the inhalation of penicillin aerosol was followed by at least minimal amounts of penicillin in the blood, indicating that the aerosol reached the alveoli.

In table 4 the serum penicillin levels are reported after the onset of nebulization of the drug in four patients with miscellaneous disease without pulmonary pathology. The excretion of penicillin in the urine is also shown. It will be observed that in these patients generally higher blood levels were found and that penicillin was obtained in the blood as early as five minutes after the onset of inhalation of the drug.



TABLE III  
Penicillin Blood Levels after Inhalation of Aerosol

Case No	Dose of Single Inhalation	Concentration Units per c c	Blood Level of Penicillin Units per c c After Inhalation						No Blood Levels
			0-15 min	30 min	45 min	1 hour	1½ to 1½ hrs	1½ hrs to 2 hrs	
1	40,000	17,000	0 004	0 02	0 01				2
2	40,000	20,000	0 01	0 07	0 02				4
3	40,000	20,000	0 02						2
4	20,000	20,000		0 01		0 01			2
5	20,000	20,000		0 02		0 02			7
6	20,000	20,000	0 02	0 14	0 14	0 07			4
7	70,000	35,000	0 02	0 02	0 004				10
8	50,000	17,000	0 004	0 02	0 09	0 04			19
9	40,000	40,000	0 09	0 18	0 02				4
10	50,000	50,000	0 03		0 02	0 02			5
11	40,000	40,000	0 01	0 03	0 01				0
12	40,000	40,000							4
13	40,000	40,000	0 02	0 25	0 01	0 01			3
14	40,000	40,000	0	0 02		0 02	0 02	±	7
15	50,000	50,000	0 03	one				±	0
16	50,000	50,000			0 02	-0 02			7
17	50,000	50,000	0 02	0 02	0 02	0 02			2
18	50,000	50,000		0 03					7
19	100,000	100,000	0 01			0 03			2
20	50,000	50,000		0 03					

The effect of inhalation of 100,000 units in 1 c c is illustrated in case D, in which the high blood level of 0 4 unit was found at five minutes, 20 minutes and 45 minutes after the beginning of aerolization of penicillin, at 105 minutes 05 unit was obtained in the sample taken at that time. This response indicates that a very high blood level can be obtained, if desired,

TABLE IV  
Blood Levels and Urinary Excretion of Penicillin during and after Inhalation of Aerosol in Subjects without Pulmonary Disease

Case No	Concentration of Penicillin Units per c c	Total Dosage Inhaled In Units	Serum Penicillin Levels After Inhalation Started (in Minutes)					
			5 to 10	15 to 30	35 to 45	50 to 65	70 to 85	90 to 105
A	40,000	40,000	1	1	05	05	0	0
	40,000	40,000	05	05		0	0	0
	40,000*	40,000		0	0	0	0	0
	100,000	50,000	0	025	0	0	0	0
B	40,000	40,000	0	0	0125	0125	0	0125
	40,000	60,000	0	0125	025			
C	40,000	40,000	025	1	05	025	025	0
	13,333	40,000	0	0	0	0	0	0
D	100,000	50,000	05	2	05	0	0	0
	100,000	100,000	4	4	4	2	1	05

\* Oropharyngeal aerosol

TABLE IV—Continued

Blood Levels and Urinary Excretion of Penicillin during and after Inhalation of Aerosol in Subjects without Pulmonary Disease

Units of Penicillin Excreted				Excretion of Penicillin During 24 Hours in Per Cent of Total				Excretion of Penicillin in Relation to Total Amount Eliminated %		
1 hour	2-6 hrs	7-24 hrs	Total	1 hr	2-6 hrs	7-24 hrs	Total	1 hr	2-6 hrs	7-24 hrs
2,940	995	250	4,185	7.4	2.5	6.3	10.5	70.2	23.8	6
431	92	0	523	1.1	2		1.3	82.4	17.6	
1,863	1,183	0	3,046	3.7	2.4		6.1	61.1	38.9	
980	2,187	539	3,706	2.5	5.5	1.3	9.3	26.5	59.0	14.5
1,418	3,675	392	5,485	2.4	6.1	7	9.2	25.8	67.0	7.2
4,620	2,703	0	7,323	9.2	5.5		14.7	63.1	36.9	
7,612	11,100	1,058	19,770	7.6	11.1	1.1	19.8	38.5	56.1	5.4

almost immediately by this method at the onset of treatment when a sufficiently large dose is used. It may also be mentioned that no sign of irritation was manifest by the patient as a result of inhaling the high concentration of 100,000 units in 1 c c. In Case A inhalation of 40,000 units in 4 c c by means of a catheter placed in the oropharynx was followed by no evidence of penicillin in the blood. In another patient treated in the same way 0.02 unit was recovered at the end of one-half hour. In the infants and children treated in this way similar small amounts of the drug (0.1 to 0.2) were found. The blood level is lower in shallow breathing, or ordinary respiration, but the local impingement of penicillin on the bronchi may be greater. A deep inspiration of 1000 c c carries most of the aerosol beyond the tracheobronchial passageway, a volume of approximately 140 c c, into the alveoli, where maximal blood absorption necessarily takes place. However, a deep breath which is held several seconds allows more penicillin to fall out of solution on both the bronchi and alveoli, with less possibility of loss in the expired air.

The excretion in the urine of penicillin during a 24 hour period following inhalation of the aerosol is shown in table 4 to vary between 10 and 20 per cent of the total amount administered. The largest percentage excretion of the drug in the urine generally takes place within the first hour in patients without pulmonary pathology, although substantial amounts are still recoverable two to six hours afterwards. Small amounts of penicillin are found in the urine from seven to 24 hours following the inhalation of the drug. Further studies are in progress in patients with bronchopulmonary disease.

It is evident that a lower excretion of penicillin takes place after administration of the drug by inhalation than by intramuscular injection. By the

TABLE V  
Effect of Inhalation of Penicillin Aerosol in Bronchial and Pulmonary Infection

Case No	Age and Sex	Diagnosis	Duration of Disease	Average Daily Dosage (Units of Penicillin)	Length of Treatment (Days)
1	35 F	Lung abscess Rheumatic heart disease Pulmonary infarction	7 weeks	200,000	8
2	36 M	Bronchial asthma Chronic bronchiolitis Pulmonary emphysema	25 years	160,000	9
3	59 F	Acute bronchitis Bronchial asthma Pulmonary emphysema	3 days (13 years)	120,000  200,000*	7  7*
4	40 F	Bronchial asthma Chronic bronchitis Pulmonary emphysema Pulmonary fibrosis	28 years	200,000	5
5	43 M	Bronchiectasis Lung abscess Pulmonary emphysema Pulmonary fibrosis	15 years	100,000	7
6	52 M	Bronchial asthma Pulmonary emphysema Pulmonary fibrosis Cardiac hypertrophy Auricular fibrillation	25 years	100,000	7
7	60 F	Bronchial asthma Bronchiolitis	8 months	250,000 200,000*	8 10*
8	24 M	Bronchiectasis Lung abscess	16 years	200,000	30
9	29 F	Bronchiectasis Pulmonary emphysema Lung abscess	23 years	148,000	35
10	61 M	Pneumonitis Lung abscess (?)	6 months	200,000	8

\* Second course of penicillin aerosol therapy

TABLE V—*Continued*

Effect of Inhalation of Penicillin Aerosol in Bronchial and Pulmonary Infection

CLINICAL COURSE AFTER PENICILLIN AEROSOL

A case of lung abscess of seven weeks' duration, treated previously for one month with intramuscular injection of 160,000 units of penicillin daily, manifested a residual cavity with fluid level. After one week of penicillin aerosol, cavity margins became indistinct, fluid level disappeared. Ultimate recovery. Penicillin intramuscularly subsequently.

Patient had had severe asthma since the age of eight, which was markedly relieved one year previously with aminophyllin and a bronchial relaxation program. Considerable cough and dyspnea on exertion remained, accompanied by both sibilant and moist râles in the lungs. After one week of penicillin aerosol therapy the symptoms were markedly improved with an increase in vital capacity from 3,800 to 4,500 c c. No change in roentgen-ray of the lungs. Three weeks later the patient developed a bronchopneumonia due to pneumococcus, was treated with sulfadiazine and recovered, although did not maintain original improvement apparently produced by penicillin aerosol.

For nine years this patient had taken hypodermic adrenalin most of the time every three to 10 hours. Following inhalation of penicillin aerosol she required no epinephrine for two months then gradual increase in cough and wheezing took place. A course of penicillin by intramuscular injection was given without improvement and a second course of penicillin aerosol for seven days was also administered with no significant improvement.

In this patient with advanced respiratory disease there was a moderate clinical improvement but an infection occurred three days after the patient left the hospital with recurrence of symptoms of cough and dyspnea.

In this patient with bronchiectasis, cavities and advanced fibrosis only little improvement took place, with an increase in vital capacity from 1,800 to 2,000 c c. The roentgen-ray before and after treatment showed no change in the lung picture.

Slight clinical improvement appeared to take place with an increase in vital capacity from 1,300 to 1,700 c c. There were fewer râles in the chest but no significant decrease in dyspnea on exertion. Roentgen-ray before and after treatment showed no change.

Striking clinical improvement followed inhalation of penicillin aerosol with marked decrease in dyspnea and in the number of sibilant and crepitant râles, vital capacity increased from 1,000 to 1,900 c c. No change on roentgen-ray before and after treatment. The patient maintained improvement for two and one-half months when cough and dyspnea and râles recurred. A second course of penicillin aerosol therapy for 10 days was followed by almost complete freedom from dyspnea, asthma and complete clearing of all râles.

No clinical improvement could be observed in this patient who had had a lung abscess and bronchiectasis for 16 years. Lobectomy was subsequently performed with recovery.

No significant improvement took place, although sputum decreased from 40 grams to 14 grams and became more fluid, with less purulent material. Cough was less frequent, but there was no change in roentgen-ray of the lungs before and after treatment.

This patient with an undiagnosed pneumonitis had had one month of intramuscular penicillin with little or no benefit. After eight days of penicillin aerosol, temperature declined from 103 to 100° F with marked clinical improvement. On discontinuance of the drug temperature recurred moderately and a course of combined aerosol and intramuscular penicillin was followed by a decline in temperature and clinical improvement with signs of clearing of infiltration by roentgen-ray.

TABLE V—Continued

Case No	Age and Sex	Diagnosis	Duration of Disease	Average Daily Dosage (Units of Penicillin)	Length of Treatment (Days)
11	60 F	Bronchiolitis Bronchial asthma Bronchopneumonia Pulmonary emphysema Pulmonary fibrosis	25 years	200,000	12
12	57 M	Bronchial asthma Bronchiectasis	18 years	200,000	7
13	62 F	Bronchial asthma Pulmonary emphysema Chronic bronchitis	25 years	200,000	7
14	62 M	Bronchial asthma Bronchiolitis Pulmonary emphysema Chronic bronchitis Bronchiectasis	20 years	200,000	8
15	42 F	Bronchial asthma Chronic bronchitis Pan-sinusitis	9 years	200,000	10
16	59 M	Bronchiectasis, bilateral, advanced Pulmonary fibrosis	7 years	200,000	5
17	56 F	Bronchiectasis Pulmonary fibrosis	5 years	200,000	6
18	53 M	Bronchial asthma Chronic bronchitis	15 years	200,000	5
19	65 M	Lung abscess, acute	5 weeks	250,000	10
20	71 F	Bronchial asthma Chronic bronchitis Sinusitis	4 years	250,000	8

TABLE V—Continued

CLINICAL COURSE AFTER PENICILLIN AEROSOL

A gradual decrease in temperature occurred over a period of six days of penicillin aerosol therapy with ultimate complete absence of cough, asthma and expectoration. Following a cold and acute sinus infection symptoms recurred one month after treatment, namely, cough, asthma and expectoration.

Striking improvement with disappearance of asthma and cough, and clearing of râles took place after seven days in a patient previously adrenalized and suffering from intractable asthma and bilateral bronchiectasis. Patient was well for one month, recurrence of symptoms was treated with penicillin by intramuscular injection for seven days and by inhalation for 12 days without improvement.\*

Moderate clinical improvement during the first six days of therapy with increased cough on the seventh day and subsequent increased betterment following one week of intramuscular penicillin. The moderate improvement obtained has persisted for three months. No change in roentgen-ray of the lungs before and after treatment.

Definite decrease in cough, expectoration and dyspnea followed inhalation of penicillin aerosol therapy. No change in roentgen-ray of lungs before and after treatment. One month later recurrence of symptoms of cough, expectoration and dyspnea took place of intensity comparable to that before penicillin-aerosol therapy.

The patient had been in the hospital for three and one-half weeks prior to treatment requiring 12 to 13 injections of adrenalin a day. However, on a bronchial relaxation program of aminophyllin and demerol the symptoms of asthma were relieved although not entirely absent prior to inhalation of penicillin aerosol. Improvement continued so that the patient required no adrenalin whatsoever, but took aminophyllin 0.3 twice daily. Symptoms of asthma continue to be absent for two months, but the result cannot be ascribed to penicillin aerosol therapy.

This patient showed no improvement from one week of penicillin injected intramuscularly nor from inhalation of neosynephrine-sulfathiazole mixture, but appeared to manifest a quite marked decrease in dyspnea and cough after four days of inhalation of penicillin aerosol. He complained of soreness in the chest at the end of five days and the treatment was stopped, the patient was discharged, temporarily improved.

This patient suffered from continuous dyspnea for five years prior to treatment and both cough and dyspnea were marked at rest. After two days of inhalation of neosynephrine-sulfathiazole mixture a definite clinical improvement took place which continued with penicillin aerosol and at the end of therapy the patient was completely relieved of shortness of breath for the first time in five years. The result was striking, but was initiated by the neosynephrine-sulfathiazole mixture and appeared to be still further benefited by penicillin aerosol. Freedom from dyspnea is still present two months later.

This patient manifested increasing cough and wheezing following an acute upper respiratory infection. On inhalation of penicillin aerosol the symptoms cleared and he left the hospital much improved. Roentgen-ray of the lungs before and after treatment showed no change. The improvement cannot definitely be ascribed to penicillin aerosol administration.

A case of acute lung abscess of five weeks' duration showed a large shadow of homogeneous density in the left hilar region in which the abscess cavity with a fluid level had become obscured. Inhalation of penicillin aerosol was promptly followed by decrease in temperature from an average of 102.5 to 100.2° F. A drop in respiratory rate from 26 to 20 and decrease in the white blood count from 25,000 to 16,000. No change in the area of pneumonitis by roentgen-ray was seen after treatment. Surgical drainage with recovery later.

Recurrent asthma for four years. Radical antral operation and vaccine therapy without benefit. For three weeks more cough and dyspnea. Improvement began with oral aminophylline and increased gradually with penicillin aerosol. Previous intramuscular injection of penicillin for eight days ineffective.

\* The notes in this case were kindly submitted by L. E. P. Eglee, who used the nebulizer with a one liter volume.

latter route 60 per cent of the penicillin injected may be recovered from the urine. However, the percentage of penicillin found in the urine is an index of the amount absorbed rather than the effectiveness of aerosol administration. In infection of the pleural cavity penicillin by systemic injection is not curative, whereas local instillation may be followed by recovery. Similarly, in lung abscess the penetration of the aerosol into the cavity may be of special value in limiting the growth of organisms.

### CLINICAL RESULTS

The clinical results of 20 patients who inhaled penicillin aerosol are summarized in table 5. The length of treatment, except in two cases, was arbitrarily set at approximately five to 10 days. The aim of the study was to explore the early response of patients with various types of bronchopulmonary infection to penicillin aerosol therapy rather than to attempt a cure of the disease process. To what extent the method itself was practical, whether the drug in this form was irritating, the degree of elevation of blood level, the effect on the pathogenic sputum organisms—these questions were considered to require an answer before a sustained therapeutic trial of penicillin aerosol could be employed. The detailed case histories are, therefore, not presented but the significant data have been included in table 5.

There were five patients in whom inhalation of penicillin aerosol was followed by a marked improvement which appeared to be attributable specifically to the drug, i.e., three with bronchial asthma, one with lung abscess and one with bronchiectasis. In Case 3 an intractable form of asthma was relieved with a marked decrease in the signs of bronchial infection. The patient had previously required adrenalin by hypodermic injection every two to six hours most of the time over a period of nine years. For two months after treatment she had no asthma. The symptoms of cough and asthma then recurred, and a second course of treatment, at first with seven days of intramuscular injection and then six days of inhalation of penicillin resulted in no significant reduction in the number of injections of adrenalin employed, although the coughing was reduced and there was no wheezing between attacks. In Case 7 a striking improvement took place, manifested by decreased dyspnea and cough, and a marked clearing not only of sibilant but also the widespread moist râles which constituted good evidence for an infectious bronchiolitis. This improvement continued for two and one-half months when cough, dyspnea and wheezing gradually returned. A second course of penicillin aerosol resulted in progressive freedom from cough and asthma, clearing of both sibilant and moist râles and a truly remarkable clinical recovery in a patient unresponsive to routine measures. In Case 10 the inhalation of penicillin aerosol was accompanied by a striking clinical improvement although previous intramuscular injection of penicillin for one month had not appeared to be of significant value. The nature of the pneumonitis and questionable lung abscess was not determined. In

Case 12, a patient with bilateral bronchiectasis and intractable asthma resistant to adrenalin, there was a striking improvement after seven days' inhalation of penicillin aerosol. The patient remained free of asthma for one month when severe attacks began again. Inhalation of penicillin aerosol for 12 days resulted in no improvement. The response to penicillin aerosol in Case 17, treated for the first two days with 0.6 per cent neosynephrine-sulfathiazole and the last five days with penicillin aerosol, was surprising. Continuous dyspnea for five years, an end result of bronchiectasis and pulmonary fibrosis, was completely relieved. Respiratory graphic tracings showed a slight increase in maximal breathing capacity (increased tidal air) after inhalation of both 1 per cent epinephrine and 1 per cent neosynephrine, but no significant elevation of vital capacity. Bronchodilator drugs were, therefore, of little if any use. The diminution of the infection, and presumably the inflammatory swelling of the bronchial wall, was followed by the clearing of a previously incapacitating dyspnea. The fact that this improvement began with inhalation of a sulfonamide aerosol (neosynephrine-sulfathiazole) is of interest, since it indicates that this method deserves a wide trial in similar cases.<sup>7b</sup> At the present time, patients in this group continue chemotherapy with sulfonamide aerosols at home, either 2.5 per cent sulfadiazine (Pickrell's solution) or neosynephrine-sulfathiazole 1.5 cc being nebulized two to four times daily.

Summarizing the cases that responded very favorably, four patients with bronchial asthma were relieved of their symptoms for one to two months. Recurrence of attacks of asthma and cough was treated by a second course of penicillin aerosol without relief in two and complete relief in two patients. The patient with bronchiectasis and pulmonary fibrosis has remained remarkably free from dyspnea since treatment, she is inhaling a sulfonamide aerosol twice daily at home. The fifth patient with undiagnosed pneumonitis and questionable lung abscess remains well now three months after treatment.

Clinical improvement of moderate degree took place in 10 cases of bronchopulmonary disease but the nature of the illness was such as to prohibit a firm conclusion of the rôle exerted by penicillin aerosol. Of these, eight had bronchial asthma with bronchial infection, and in addition either pulmonary emphysema or bronchiectasis of some degree. Their course is summarized in table 5 (Cases 2, 4, 11, 13, 14, 15, 18, and 20). Recurrence of symptoms took place in four of eight of these improved cases within a period of approximately one month after five to eight days of inhalation of penicillin aerosol. Of the remaining three cases in this group one (Case 1) was that of lung abscess, and the roentgen-ray change in her case appeared to indicate a definitely favorable influence of penicillin administered through the lungs as compared to intramuscular injection. Another was a case of advanced bilateral bronchiectasis who was apparently temporarily improved (Case 16). Of the five remaining cases, one patient had a lung abscess with a closed cavity. Although the fever declined, there was no other significant



change in his clinical condition. Two long-standing cases of bronchiectasis with chronic lung abscess (Cases 8 and 9) and two cases of advanced pulmonary fibrosis were not significantly benefited. In no instance did the patient appear to be influenced adversely by penicillin aerosol therapy.

In addition to the adult group discussed above, five children with staphylococcus bronchitis, developing in association with congenital pancreatic deficiency, have been treated with inhalation of penicillin aerosol, for the most part by means of a catheter inserted in the oropharynx and more recently by inhalation with a mask rebreathing nebulizer apparatus (These cases will be reported separately in detail by Dr Dorothy H Andersen). Previous treatment of this type of disease by intramuscular injection of penicillin was tried on three patients in 1943 with temporary benefit only. Of the five cases treated by inhalation of penicillin aerosol with a dosage of 32,000 units per day for eight to 10 days, there was definite improvement in three patients. One patient, who was gravely ill with high fever, marked dyspnea and cyanosis, was dramatically improved after the inhalation of penicillin aerosol. The problem of technic of administration of aerosol to children is being studied at this time, and further trials of various methods are in progress. Culture of the nasopharynx showed a disappearance of *Staphylococcus aureus* in three patients tested before and after inhalation of penicillin aerosol.

#### DISCUSSION

In appraising the value of administration of penicillin through the lungs a primary consideration is that of the safety of the method itself. Although the lungs of the 19 rats exposed to repeated inhalations of penicillin aerosol showed on microscopic section an increased incidence of scattered areas of congestion and edema, as compared to the lungs of the control animals, these changes were slight. Furthermore, the bronchi were entirely normal. The control animals were not treated with inhalation of normal saline and the possibility presents itself that such changes as were found may have been due to the fact that the animals were held with their heads in glass "helmets" and inhaled a considerable volume of fluid in the form of a nebulin. The differences between the two groups did not appear to be significant.

In 20 patients who were treated for seven days to one month there were four who manifested one or more of the following possible side-effects of the drug. Increased cough in one patient was noted at the end of a week of inhalation of penicillin aerosol. In three patients a sensation of substernal soreness was present for the better part of one day and then disappeared. The patient who had initially shown a decrease in peribronchial markings revealed at the end of one month of inhalation of penicillin aerosol a slight increase in peribronchial infiltration. The possible irritant effect of the drug may be considered as either slight, or negligible,

since the remaining patients in this series manifested nothing that could be interpreted as an irritant effect either clinically or by roentgen-ray before and after treatment. Furthermore, the seriousness of the clinical situation in the majority of patients treated would outweigh our questionable evidence for irritation as the result of inhalation of penicillin aerosol.

The fact that rats could be protected against an intraperitoneal injection of hemolytic streptococcus culture by inhalation of penicillin aerosol demonstrates that the drug is absorbed and therapeutically effective in combating systemic infection if an adequate dosage is administered. Since the heads of the rats were in a glass helmet and the penicillin aerosol was nebulized continuously by a flow of 4 liters per minute of oxygen, a considerable loss of the drug inevitably took place. In one group of four rats that were killed one-half hour after inhalation of 20,000 units of penicillin aerosol and whose blood was pooled for determination of the level of penicillin, 0.004 unit was found. Despite this minimal blood level approximately 50 per cent of rats may be protected by inhalation of penicillin as an aerosol.

The determination of the blood levels in the patients treated in this series revealed lower levels of penicillin than would be obtained by a comparable dosage administered intramuscularly. Higher blood levels can be obtained when the patients take a deep inhalation and hold the breath for several seconds. It may be observed that the mist of penicillin aerosol is not visible in the expired air under these circumstances, although it is readily seen if respiration is allowed to proceed normally. In the treatment of infection in the bronchial wall a local application of penicillin is the aim of treatment rather than a high blood level. However, deep inhalations and breath-holding are probably desirable even when the treatment of bronchial infection is intended. It may be ultimately discovered that a combination of penicillin injected intramuscularly, to provide a high blood level, and inhalation of penicillin aerosol will be the procedure of choice in patients with bronchiectasis or chronic bronchitis and bronchial asthma. In patients with lung abscess this may also prove to be the most effective procedure.

Since the penetration of penicillin aerosol into the abscess cavity is dependent upon its communication with a bronchus, deep inhalation would appear to be desirable in order to increase the lumen of the bronchi, and in that way facilitate entrance of penicillin into the cavity. Since it is known that injection of penicillin either intramuscularly or intravenously does not result in cure of empyema and that local instillation of the drug is often therapeutically successful, an argument can be made by analogy that local deposition of penicillin in a lung abscess may be of special value. The clinical response in the two cases that had previously received penicillin by intramuscular injection for one month offers merely suggestive evidence in this respect. However, one of these patients appeared gravely ill with severe dyspnea in an oxygen tent at the time penicillin aerosol administration was commenced. A week later the patient's temperature had decreased

from 103° F to 100° F, and there was coincident striking clinical improvement. This apparent response to inhalation of penicillin aerosol justifies the suggestion that this procedure be tried in other cases of acute lung abscess either in conjunction with or without intramuscular injection of penicillin.

Although the immediate response to inhalation of penicillin aerosol revealed the disappearance of the predominating organisms in the sputum culture, further evidence is needed concerning the duration of absence of pathogenic organisms. In all likelihood a longer period of treatment will be required to overcome chronic infection in the bronchial wall. The recurrence of symptoms in three of five patients who were strikingly improved and four of eight who appeared moderately improved offers the opportunity of testing the effectiveness of the procedure itself. In two patients a second course of treatment was completely successful. The duration of treatment as well as the most efficient form of proceeding in administration of penicillin in cases of this type requires further investigation. The apparatus for automatic delivery of penicillin during the inspiratory cycle is now being tried clinically.

Additional studies are needed to determine the optimum dosage. It has been shown that it is clinically feasible to administer 40,000 to 50,000 units of penicillin in 1 c.c. of normal saline, four to five times daily. The nebulizer made by the Vaponefrin Company and the No. 40 type of the DeVilbiss Company produce particles that are mostly smaller than 1 micron in diameter. Particles of this size penetrate into the lungs and are less apt to be deposited on the tracheobronchial tree than those of larger size. It may ultimately be found that a range of particle size somewhat larger than that produced in this type of nebulizer may be an advantage. However, the fact that larger particles may be lodged on the larynx and trachea would be a disadvantage since they would contain the major portion of penicillin. (The plastic nebulizers made by the Vaponefrin Company and the Nephron Company appear to be the best of this type.) The addition of a large bulb of 1000 c.c. capacity attached to the upper surface of the Vaponefrin nebulizer has the function of serving as a reservoir for some of the exhaled air which contains a moderate amount of penicillin in ordinary breathing.

The maintenance of a blood level as high as 0.4 unit as a result of deep breathing was shown in the patient who inhaled 100,000 units in 1 c.c. If a high blood level were desired in emergency situations in which repeated intramuscular injections were not feasible, the procedure of inhalational absorption of penicillin could be carried out. Although the method is not to be considered as a potential replacement of systemic administration of this drug, situations may occur in which the inability to secure either a doctor or a nurse for injection of penicillin might be handled by administration of penicillin aerosol in relatively large doses. Since the dosage for

injection of penicillin intramuscularly has been well established, it should be given in this way whenever it is possible to do so

### SUMMARY AND CONCLUSIONS

The inhalation of penicillin aerosol as a clinical therapeutic procedure was studied from various points of view

In respect to its possible irritant effect on the lungs, in concentrations between 5,000 to 50,000 units per c c, the lungs of 19 rats, exposed to repeated inhalations of the drug, were compared to those of control animals. The differences on microscopic section were not considered significant, although the incidence of congestion and other changes was slightly greater in the treated animals. Administration of penicillin aerosol to 20 patients for seven days to one month offered no convincing evidence of an irritant effect on the lungs. A sensation of substernal soreness was experienced by three patients for one day or less. Inhalation of 20,000 to 100,000 units per c c in 10 normal and miscellaneous controls did not result in a subjectively perceived irritant effect.

Rats were protected against intraperitoneal injection of hemolytic streptococcus culture by a single inhalation of 25,000 units of penicillin aerosol. The head of the rat was enclosed in a glass helmet into which a continuous stream of aerosol was delivered.

In human subjects the penicillin solution was aerosolized by the passage of 5 to 8 liters per minute of oxygen through a nebulizer containing 1 c c of penicillin in concentrations between 20,000 and 100,000 units per c c. By means of a Y tube between the oxygen regulator and the nebulizer, the penicillin was aerosolized only during the inspiratory cycle. When a 1000 c c glass bulb is fused to the upper surface of the nebulizer some of the penicillin in the exhaled air is re-inhaled. This modification is not essential but permits a greater economy in the use of the drug than the standard nebulizer. An apparatus which provides penicillin aerosol during the inspiratory cycle only without the need of the patient's cooperation is being tried at this time.

An exploratory study of the effectiveness of penicillin aerosol therapy in 20 patients with bronchopulmonary infection revealed (1) the predominating organisms in the sputum culture were consistently absent 24 hours after discontinuance of treatment, (2) the blood level of penicillin for one hour following inhalation of the aerosol was generally between 0.01 and 0.04 unit, at times as high as 0.18. In a patient without pulmonary pathology, in whom deep breaths were taken during the inhalation of 100,000 units in 1 c c, a blood level of 0.4 was obtained for one hour, in this patient 20 per cent of the inhaled penicillin was recovered in the urine. The aim of treatment, however, is generally not a high blood level but a local application of penicillin on the bronchial wall.

The results are to be considered in the light of an arbitrarily imposed

limit of treatment, as well as a varied pathology. The 20 cases treated suffered from (a) varying combinations of bronchial asthma, bronchiectasis, and pulmonary emphysema, (b) bronchiectasis with and without chronic lung abscess, (c) pulmonary fibrosis and emphysema, (d) acute lung abscess. In five patients the improvement was marked and seemed definitely the effect of inhalation of penicillin aerosol. In 10 others improvement was moderate, and in the remaining five cases no significant clinical benefit was achieved. Of the 15 improved cases, seven suffered a recurrence of symptoms in two months or less. Further studies on the effect of penicillin aerosol are indicated in (a) bronchial asthma with bronchial infection, (b) bronchiectasis, and (c) acute lung abscess.

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# PENICILLIN THERAPY AT THE UNIVERSITY OF MINNESOTA HOSPITALS· 1942-1944

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ON July 9, 1942, J E , a seven year old girl, entered the University Hospitals Two days later, she received penicillin because of a severe staphylococcic bacteremia, with 68 colonies of coagulase-positive staphylococci per cubic centimeter of blood Pneumonia and an acute osteomyelitis of the left femur were also present Her general condition improved rapidly This patient was the first to receive penicillin at the University Hospitals Since that time, over a period of two years, a total of 200 patients have received penicillin under our supervision The purpose of this report is not to review the voluminous literature on penicillin, but to present the types of infections treated, the results of therapy, and to discuss briefly some of the clinical problems relating to this new chemotherapeutic agent Although a majority of the patients were treated at the University Hospitals, several important types of infections were treated in other institutions through the cooperation of physicians in Minneapolis and St Paul This applies particularly to a group of infants and children treated at the Abbott Hospital in Minneapolis with the aid of Dr Georgie M Burt, Resident in Pediatrics

In every instance an attempt was made to isolate the etiological agent from the local lesions or the body fluids before treatment was undertaken Dr Gerald Needham, Head of the Bacteriological Laboratories at the University Hospitals, was most helpful in this respect The types of infections treated during a period of two years are summarized in table 1

One hundred and ninety of the patients received the sodium salt of penicillin, and 10 had the calcium salt administered to them There did not appear to be any essential difference in the therapeutic response of the patients to either one of the salts The material was injected parenterally, and in a few instances, applied locally to infected wounds or burns When administered parenterally, the intravenous or intramuscular routes were employed None was given subcutaneously The material was dissolved in sterile physiological saline solution and given as an intravenous drip, or as

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TABLE I

Summary of Types of Infections Treated with Penicillin

	No. of Cases
<i>Staphylococcic Infections</i>	
Staphylococcic bacteremia without osteomyelitis	20
Staphylococcic bacteremia with osteomyelitis or suppurative arthritis	8
Acute staphylococcic osteomyelitis or suppurative arthritis without demonstrable bacteremia	3
Chronic staphylococcic osteomyelitis without demonstrable bacteremia	13
Staphylococcic infections without demonstrable bacteremia	13
<i>Streptococcic Infections</i>	
Hemolytic streptococcic bacteremia	7
Streptococcic infections without demonstrable bacteremia	12
<i>Meningitis</i>	
Pneumococcic	14
Meningococcic	10
Staphylococcic	3
<i>Pulmonary Infections</i>	
Pneumococcic pneumonia without empyema	9
Non-pneumococcic pneumonia without empyema	11
Empyema	10
<i>Subacute Bacterial Endocarditis and Endarteritis</i>	10
<i>Sulfonamide Resistant Gonorrhea</i>	16
<i>Gonorrhea with Arthritis</i>	4
<i>Genitourinary Tract Infections</i>	22
<i>Miscellaneous Infections</i>	15
	<hr/> 200

intermittent intravenous or intramuscular injections. In a few instances, the penicillin was dissolved in sterile distilled water with 5 per cent dextrose. The local application was made with saline solutions of penicillin containing 250 to 500 units per cubic centimeter or with an ointment having 500 units per gram.

## RESULTS OF TREATMENT

### Staphylococcic Infections

Fifty-seven patients had infections due to staphylococci. It is significant that in recent years more cases of staphylococcic sepsis have been seen at the University Hospitals than instances of streptococcic disease. This probably is due in part, at least, to the fact that physicians throughout the State have succeeded in controlling many streptococcic infections with sulfonamide therapy. On the other hand, as is generally agreed, the sulfonamides are not so effective in the treatment of staphylococcic infections. For purposes of a more critical analysis, the cases of staphylococcic sepsis have been divided into several groups.

*Staphylococcic Bacteremia With and Without Osteomyelitis* Cases of staphylococcic bacteremia without primary or metastatic bone lesions have been separated from those having osteomyelitis or suppurative arthritis be-



cause in our experience and those of others the mortality rate of the former group has been shown to be definitely higher than in those with osseous complications. It is generally accepted that the mortality rate of untreated cases of staphylococcic bacteremia varies between 61 and 91.4 per cent. There is considerable evidence that the use of the sulfonamides, particularly sulfathiazole, has reduced this mortality rate in recent years, but the results, in general, have not been satisfactory.

Twenty patients having bacteremia without osteomyelitis due to coagulase-positive staphylococci were treated with penicillin. Of this group, 13 recovered and seven died, giving a mortality rate of 35 per cent as noted in table 2. An analysis of the fatal cases indicates that three patients re-

TABLE II  
Acute Staphylococcic Bacteremia  
Results in 28 Patients Treated with Penicillin

	No. of Cases	Recovered	Died	Mortality Rate
Without osteomyelitis or arthritis	20	13	7	35%
With osteomyelitis or arthritis	8	7	1	12.5%

ceived inadequate doses of penicillin, two patients had an acute staphylococcic endocarditis, and two patients received what is considered to be sufficient penicillin but a bacteremia was still present at the time of death. Of the patients who recovered, there were four infants under 12 months of age. The youngest patient was 12 days old. In general, the therapeutic results with the entire group were considered to be more satisfactory than those obtained with the sulfonamides.

Of the eight patients having staphylococcic bacteremia with osteomyelitis or suppurative arthritis, seven recovered. The one fatal outcome occurred in an individual with an acute staphylococcic endocarditis of the mitral valve. The results of treatment with penicillin upon the bone lesions will be discussed shortly.

Although varying doses of penicillin were used in the 28 patients having bacteremia, a general statement concerning dosage schedules may be made. In the present investigation, the purpose has been to clear the blood stream of organisms as soon as possible, and also to sterilize any primary or metastatic foci. In the zeal to accomplish these ends, larger doses than the minimal requirements may have been used. There still exists divided opinion among reliable investigators concerning optimal doses. Our policy is to use large initial doses, preferably by means of an intravenous drip, and then to give subsequent smaller doses intermittently by the intramuscular route.

*Doses of Penicillin for Infants* An initial dose of 10,000 units may be given in an intravenous drip using 150 c.c. of physiological saline solution. As much as 25,000 units have been given in this manner. Because of the

difficulties often associated with administering intravenous solutions to infants, a practical and successful method of giving penicillin is to inject 5,000 units of penicillin contained in 0.5 c.c. saline solution intramuscularly every two to three hours until the infection is brought under control. Then 2,000 to 2,500 units may be given intramuscularly every three hours until the temperature remains normal. The maximal total dose was used in an infant 12 days old, and amounted to 755,000 units given over a period of 20 days.

*Doses of Penicillin for Adults* The procedure, used with satisfactory results, has been that of injecting 20,000 units intramuscularly every two hours for at least the first 24 hours, and then 10,000 to 15,000 units every three hours thereafter until the infection has been brought under control. Patients seriously ill and often dehydrated have been given 50,000 to 100,000 units as an intravenous drip over a period of 10 to 12 hours, utilizing a liter of physiological saline solution for this purpose. This dose has been repeated every 10 to 12 hours for several doses. After initial doses of this magnitude, 15,000 to 20,000 units have been given intramuscularly every three hours until the temperature has remained normal or the infection has been brought under control. The total dose employed has approximated one million units. Obviously, any foci should be drained surgically when indicated. In patients having bacteremia associated with osteomyelitis, the schedule of doses used has been approximately the same as employed for bacteremia without osteomyelitis except therapy was continued for a longer period of time resulting in a larger total dose of penicillin. The patients with osseous lesions received between two and three million units of penicillin.

*Acute and Chronic Staphylococcic Osteomyelitis or Suppurative Arthritis* The therapeutic results with 24 patients who received penicillin are shown in table 3. Twenty-two of these patients had osteomyelitis of the long

TABLE III  
Staphylococcic Osteomyelitis or Arthritis  
Results in 24 Patients Treated with Penicillin

	No. of Cases	Improvement	Complete Recovery	No Improvement
Acute osteomyelitis	8	4	3	1
Acute suppurative arthritis	3		3	
Chronic osteomyelitis	13	8	2	3

bones, one had osteomyelitis of the ribs, and three had an acute suppurative arthritis.

Six of the eight patients with acute osteomyelitis had a demonstrable staphylococcic bacteremia. As already stated with reference to table 2, one of these patients died because of acute staphylococcic endocarditis. Of the remaining five patients having acute osteomyelitis with bacteremia, only

one, a three year old child, has had a complete recovery. In this instance, a recent roentgenogram of the left femur shows evidence of considerable bone destruction and new bone formation. In four patients signs of active osteomyelitis persisted after therapy had been discontinued.

Three patients who had acute staphylococcic arthritis had no evidence of infection after the completion of therapy. Two had an early suppurative process of the hip and bacteremia, and recovered completely. One case of suppurative arthritis of the right elbow recovered with a residual limitation of motion of the joint after 1,415,000 units of penicillin had been administered.

Two patients having acute osteomyelitis without bacteremia recovered completely. One of these individuals had a lesion of the neck of the right femur, and seven months after receiving 1,260,000 units of penicillin in 18 days, there is no evidence of a residual infection. The second case had a suppurative pericarditis and empyema in addition to osteomyelitis of the right tibia. Fifteen months after receiving 1,195,000 units of penicillin, there are no signs of bone infection.

Thirteen cases of chronic osteomyelitis have received penicillin. Two of the patients apparently have recovered completely, eight patients had temporary improvement, and three persons showed no improvement.

In summarizing the results of therapy with penicillin in a small series of cases, it may be stated that complete recovery was effected in less than one half the cases of acute osteomyelitis. Although clinical improvement occurred in the remaining cases, staphylococci have been cultured from draining lesions months after the completion of treatment. The results with chronic osteomyelitis revealed that only two of 13 patients have recovered completely from their infection. It is possible that a total dose of two to three million units of penicillin is inadequate for the treatment of osteomyelitis. It appears quite likely that surgical intervention in conjunction with penicillin therapy will yield better results, particularly in the treatment of chronic osteomyelitis of the long bones. More recently, another therapeutic attack against chronic osteomyelitis is being evaluated in cooperation with Dr. Clarence Dennis of the Division of Surgery. A total of one to two million units of penicillin is being administered parenterally. Then surgical removal of any sequestrum is carried out, and the infected bone is saucerized. If in vitro tests reveal that the offending strain of staphylococcus is sensitive to sulfathiazole, crystals of this compound are placed in the saucerized bone before closing the wound. Penicillin is then administered postoperatively for a total of one to two million units.

*Staphylococcic Infections Without Demonstrable Bacteremia* Sulfonamide therapy had been used in this group of 13 patients, prior to the administration of penicillin. There were four individuals with suppurative otitis media and mastoiditis. Two children in this group recovered completely in a short period of time after receiving 205,000 and 525,000 units of penicillin. In two adults, it was necessary to perform mastoidectomies before

TABLE IV  
Staphylococcic Infections without Bacteremia  
Results in 13 Patients Treated with Penicillin

	No of Cases	Improvement	Complete Recovery	No Improvement
Otitis media and mastoiditis	4	2	2	
Sinusitis	1	1		
Soft tissue infections	8	2	2	4

the infections were completely eradicated. One infant with staphylococcic sinusitis exhibited improvement, but not complete recovery, after receiving 475,000 units.

The remaining eight patients had infections of the soft tissues. Penicillin was applied directly to the lesions in five of the eight patients. One patient with extensive third degree burns failed to improve, and a second individual with multiple subcutaneous abscesses had only temporary improvement. In the other three patients, local therapy was combined with parenteral treatment, followed by slight to definite improvement. Of the remaining three patients, one recovered completely from a bilateral orbital cellulitis, one diabetic adult with multiple subcutaneous abscesses recovered completely, whereas a third individual with an abscess of the thigh failed to respond to penicillin.

### Streptococcic Infections

*Hemolytic Streptococcic Bacteremia* Like staphylococcic bacteremia, the mortality rate of untreated patients with bacteremia due to hemolytic streptococci is over 70 per cent, but unlike staphylococcic bacteremia, the sulfonamide compounds have decidedly reduced this mortality rate. As shown in table 5, seven patients with hemolytic streptococcic bacteremia were treated

TABLE V  
Streptococcic Infections  
Results in 19 Patients Treated with Penicillin

	No of Cases	Complete Recovery	Improvement	No Improvement	Died
Hemolytic streptococcic bacteremia	7	3			4
Hemolytic streptococcic soft tissue infections	2	2			
Streptococcic sinusitis	3	2	1		
Streptococcic otitis media	3	3			
Streptococcic otitis media with mastoiditis	4	1	3		

with penicillin. Three of the patients recovered, and four died, but an analysis of the fatal cases revealed that in every instance the blood stream was rapidly cleared of organisms, and death was attributed to other factors. One patient died because of an aplastic anemia, one had acute lymphatic leukemia,

a third fatality was due to a pulmonary embolism, and the fourth patient apparently recovered from a severe streptococcic bacteremia, and died several days later from causes which were not clearly established even after a complete postmortem examination

The doses of penicillin required for the treatment of streptococcic bacteremia were less than those used in patients with staphylococcic bacteremia. This may be related to the fact that most strains of hemolytic streptococci are more sensitive to the antibacterial action of penicillin than are staphylococci. Usually, the bacteremia may be eradicated by giving 20,000 units intramuscularly every two to three hours for 24 hours, and then 10,000 to 15,000 units every three hours for a few days thereafter. The total dose required will depend upon the nature of the primary or metastatic lesions, and whether they are amenable to surgical drainage. The maximum dose used was one million units.

*Streptococcic Infections Without Demonstrable Bacteremia* Twelve patients are included in this group, three of them having infections due to non-hemolytic streptococci. Two individuals had chronic lesions of the soft tissues which had been treated with the sulfonamides. Rapid recovery followed the parenteral use of penicillin. Two patients had a severe and acute sinusitis with osteomyelitis of the frontal bones due to hemolytic streptococci. Complete recovery followed therapy with penicillin. One patient had an acute sinusitis with orbital abscesses due to non-hemolytic streptococci. Recovery was gradual but complete after the use of over one million units of penicillin. Three patients had a suppurative otitis media, and observation of these cases indicates that treatment with penicillin is associated with rapid and complete recovery. Four patients had a suppurative otitis media with mastoiditis. Treatment with penicillin was followed by complete recovery in one instance. The other three patients improved, but mastoidectomies were necessary. The doses of penicillin used in all of the foregoing cases were essentially the same as used in the treatment of the patients with bacteremia.

It would appear from clinical observations and in vitro tests that some strains of non-hemolytic streptococci are more resistant to penicillin than the Lancefield group A hemolytic streptococci.

In connection with hemolytic streptococcic diseases it should be pointed out that *after* the establishment of an infection the administration of penicillin will not prevent the development of acute rheumatic fever. Furthermore, therapy with penicillin is contraindicated as specific treatment for acute rheumatic fever.

### Meningitis

A total of 27 patients with bacterial meningitis have been treated with penicillin. The types of meningitis and the results of therapy are shown in table 6.

TABLE VI  
Meningitis  
Results in 27 Patients Treated with Penicillin

	No of Cases	Recovered	Died	Mortality Rate
<i>Meningococcic</i>	10	9	1	10%
<i>Pneumococcic</i>	14	11	3	21%
<i>Staphylococcic</i>	3	2	1	33 $\frac{1}{3}$ %

*Pneumococcic Meningitis* This is a serious form of meningitis with a uniformly fatal outcome in untreated cases. Even with the use of the sulfonamides and type specific antipneumococcic serums mortality rates ranging from 60 to 80 per cent have been reported. It would appear that these rates may be reduced considerably following the administration of penicillin. Fourteen patients have received penicillin followed by 11 recoveries. This yields a mortality rate of 21 per cent. If the death of one patient is discounted because penicillin was not injected intrathecally, the mortality rate in the remaining 13 individuals is 15 per cent. Operative procedures carried out in this group include mastoidectomy in three patients, and myringotomy in four. Although sulfonamide therapy was employed concurrently in several patients, it is difficult to assay the value of this procedure. Five infants under 12 months of age were treated and all recovered. Of the three fatal cases, one died because of acute heart failure due to an acute aortic endocarditis with rupture of an aortic cusp, but without evidence of meningitis. The other two fatal cases were due to meningitis.

In small infants, the dose of penicillin was 2,500 to 5,000 units intramuscularly every three hours, and 2,000 to 5,000 units of penicillin in 5 cc of physiological saline solution injected intrathecally every 12 to 24 hours. The total dose used was from 300,000 to 500,000 units. For adults, initial doses of 50,000 to 75,000 units of penicillin were given intravenously as a continuous drip for 12 hours in one liter of physiological saline solution. This was repeated for two to three doses in several instances. Then the patients were given 10,000 to 15,000 units intramuscularly every three hours. From 10,000 to 15,000 units in 10 cc of physiological saline solution were injected intrathecally every 12 to 24 hours until the fluid became sterile and clear. In a few instances, the penicillin was injected directly into the cisterna magna. The total dose of penicillin approximated one million or less units.

*Meningococcic Meningitis* Although this type of meningitis generally responds quite satisfactorily to sulfonamide therapy, a group of unusually severe cases was seen and treated in cooperation with the Staff of the Division of Neuropsychiatry at the University Hospitals. Dr. A. B. Baker classified some of the patients as having meningo-encephalitis due to the meningococcus. Sulfonamides had been employed without entirely satisfactory results, and, therefore, penicillin was administered. Ten cases were

treated and nine patients recovered. One adult with a block in the intrathecal space failed to respond and died. The same routine was used in treating these patients as detailed for the therapy of pneumococcic meningitis with the exception that the total dose of penicillin was approximately 50 to 75 per cent of that used for pneumococcic meningitis, and the total number of intrathecal injections was less.

*Staphylococcic Meningitis* Three infants were treated and two recovered. One infant, three weeks of age, received a total of 199,000 units in 20 days, in doses of 1,000 units intramuscularly every three hours, and 2,000 units intrathecally daily for 19 days. A second infant, two months old, received 1,096,500 units in 54 days with 3,000 units given intramuscularly every three hours and 3,000 units injected intrathecally every 12 hours. Both of these patients recovered but during therapy developed epidural abscesses at the site of the intrathecal injections. This complication was cured by injecting penicillin directly into the abscesses. A third infant with a meningo-myelocoele died with a meningitis due to *E. coli* and staphylococci. Sulfadiazine was also administered. Staphylococci disappeared from the cerebrospinal fluid but the *E. coli* persisted.

### Pulmonary Infections

Penicillin has proved to be highly effective in the treatment of certain types of infections involving the respiratory tract and pleural cavities. Thirty patients are included in this group of patients. For purposes of discussion, the cases are divided into four groups as given in table 7.

TABLE VII  
Pulmonary Infections  
Results in 30 Patients Treated with Penicillin

	No. of Cases	Complete Recovery	Improvement	No Improvement	Died
Bacterial pneumonia (non-pneumococcic)	9	4	3	1	1
Non-putrid lung abscess	2	2			
Pneumococcic pneumonia	9	5			4
Empyema	10	8	1		1

*Bacterial Pneumonia (Non-pneumococcic)* Nine patients, who had evidence of a bacterial type of pneumonia but not proved to be pneumococcic in origin, were treated. One of the nine patients died. In this case, Gram positive diplococci were recovered from the sputum, but routine typing with antipneumococcic sera failed to show a specific reaction. The patient did not respond to penicillin, and postmortem examination revealed an acute endocarditis of the aortic valve. Three other patients, with similar bacteriological data, recovered. One patient with a mixed flora of bacteria in the sputum, failed to improve, and subsequently, bilateral pulmonary tuberculosis was shown to be present. Of four cases with staphylococcic pneu-

monia, three recovered completely and one was markedly improved following treatment with penicillin. One patient having an involvement of all five lobes due to non-hemolytic and hemolytic streptococci failed to improve with penicillin, but concurrent therapy with sulfamerazine resulted in a slow and complete recovery. One patient with staphylococci and non-hemolytic streptococci in the sputum improved slowly.

The schedule of doses used in the foregoing patients was essentially the same as employed for individuals with pneumococcic pneumonia, except that the total doses were greater.

*Non-putrid Lung Abscesses* Two patients were treated successfully. Both had previously received sulfonamides without improvement. One adult had multiple pulmonary abscesses due to staphylococci, bilateral pleural effusion, and possibly a brain abscess. After receiving 2,452,000 units of penicillin over a period of 33 days, he recovered completely. A second patient had a large pulmonary abscess with non-hemolytic and hemolytic streptococci, and coagulase-positive staphylococci in the sputum. After one course of penicillin totalling 1,205,000 units and given in 22 days, he was markedly improved. A relapse ensued, however, and an additional 1,795,000 units were injected over a period of 40 days. This patient recovered completely.

It would appear that in the treatment of the less acute cases of pulmonary suppuration with penicillin it may be necessary to treat such patients for several weeks.

*Pneumococcic Pneumonia* The mortality rate of pneumococcic pneumonia has been markedly reduced as a result of sulfonamide therapy. It would appear that all types of pneumococci are sensitive to penicillin. Although physicians may still obtain satisfactory clinical results with the sulfonamides, penicillin is indicated for use in those patients not responding to a sulfonamide. On the other hand, as our data with a small group of patients illustrate, fatalities may be anticipated even with penicillin available. It is apparent that the indications for the use of specific antipneumococcic serum in the treatment of pneumococcic pneumonia are growing less and less.

In the present series of cases, nine patients with pneumococcic pneumonia, four of whom had demonstrable bacteremia, were treated with penicillin, and five patients recovered. Of the fatal cases, one showed no improvement, having a persistent bacteremia, and death was presumably due to acute pneumococcic endocarditis. A second patient apparently had recovered from pneumonia and death was ascribed as being due to ventricular fibrillation. A third patient with a pneumonia due to type XXXIII pneumococci failed to respond and died because of a complicating diabetic acidosis and nephrosis. A fourth patient with a postoperative pneumococcic pneumonia improved, but died as a result of a splenectomy.

Relatively small total doses of penicillin suffice for the treatment of pneumococcic pneumonia. Satisfactory results have been obtained with



500,000 units Fifteen thousand to 20,000 units given intramuscularly every two to three hours will usually cause a drop in temperature and clinical improvement within the first 24 hours Subsequent treatment calls for 10,000 units every three hours for two or three days Patients with pneumococcic pneumonia often require parenteral fluids, and penicillin may be given intravenously in the form of a continuous drip utilizing 50,000 units in a liter of physiological saline solution

*Empyema* Suppuration of the pleura due to pyogenic cocci has not responded very satisfactorily to sulfonamide therapy In many instances, surgical drainage of the pleural cavities has been necessary The results in 10 patients would indicate that more satisfactory responses will be forthcoming with penicillin There were six patients who had coagulase-positive staphylococci in the purulent empyema fluid In five of the six patients, the infection was controlled and complete recovery effected following the introduction of penicillin directly into the pleural spaces The sixth patient had an infection due to staphylococcus, type XX pneumococcus and *Aerobacter aerogenes* Penicillin succeeded in eradicating the pneumococci and staphylococci, but the *Aerobacter aerogenes* persisted in the aspirated material Open drainage of the pleural cavity was necessary, but the patient eventually died because of an aspiration pneumonia In the treatment of staphylococcic empyema, the total amount of penicillin to be employed, the quantity to be injected intrapleurally, and the question of simultaneous parenteral penicillin therapy depend upon the age of the patient, the size of the empyema cavity, and the clinical condition of the patient Thus in an infant three weeks old with a right pyopneumothorax, a total dose of 97,250 units was used Three thousand units were placed in the pleural cavity every 24 to 48 hours, and the material was also administered parenterally The patient recovered completely In adults, from 10,000 to 100,000 units in up to 200 cc of physiological saline solution have been introduced intrapleurally every day Prior to each injection, as much of the fluid as possible was removed with a needle and syringe It was surprising in some instances how long the empyema fluid continued to contain staphylococci, and only persistent treatment finally brought the infection under control In most instances, penicillin was also administered parenterally in doses of 10,000 to 15,000 units every three hours because of the patient's general condition The total amount of penicillin used in the treatment of staphylococcic empyema was approximately one million units

One patient with an empyema due to streptococci of the viridans type improved with sterilization of the empyema fluid, but open drainage was necessary to close the cavity Another patient having empyema due to a non-hemolytic streptococcus recovered completely This also applies to an empyema due to type I pneumococci Another patient with an encapsulated mediastinal empyema due to hemolytic streptococci recovered almost dramatically after 100,000 units of penicillin were injected intrapleurally on two occasions

## Subacute Bacterial Endocarditis or Endarteritis

Subacute bacterial endocarditis is practically a uniformly fatal disease, and only rarely has therapy with the sulfonamides provoked a remission. Surgical intervention in cases of patent ductus arteriosus with subacute bacterial endarteritis has been followed by complete remissions and probable cures. Apparently a more hopeful outlook may be anticipated in patients with subacute bacterial endocarditis following the continuous administration of large doses of penicillin. Even here, however, a reasonable lapse of time is necessary before final conclusions may be drawn. Eight cases of subacute bacterial endocarditis and two cases of patent ductus arteriosus associated with bacterial endarteritis have been treated with penicillin at the University Hospitals. Heparin has not been employed as an ancillary therapeutic agent. We cannot subscribe to the use of heparin or any other anticoagulant in patients with bacterial endocarditis. A fatal cerebral hemorrhage was induced in two patients when sulfapyridine was administered along with heparin.

Of the eight patients having subacute bacterial endocarditis, each of four individuals received less than one million units of penicillin without benefit. The four remaining patients received 4,200,000 units given in doses of 120,000 units every 12 hours as a continuous intravenous drip. The penicillin was dissolved in either one liter of physiological saline solution or one liter of sterile distilled water containing 5 per cent dextrose. One patient was not improved and an autopsy revealed bacterial vegetations with ulceration of both the aortic and mitral valves. A second patient had a remission in fever and blood cultures remained sterile, but death at the conclusion of therapy was due to peritonitis following rupture of a huge abscess of the spleen. A large vegetation on the mitral valve contained viable *Streptococcus viridans*. A third patient appeared to be in complete remission but his cardiac reserve was very low and he died five weeks after the completion of therapy because of heart failure. There was only a small vegetation a few millimeters in size on an aortic leaflet but a rupture of a chorda tendineae had taken place because of a small ulcerative vegetation. However, *Streptococcus viridans* was recovered from the vegetations. A fourth patient had a remission for four weeks following the completion of treatment. At the end of this period he had a relapse with bacteremia, fever, and embolic phenomena.

One patient had a ligation of a patent ductus arteriosus. Two months following operation the murmur reoccurred, probably due to recanalization, and the signs of acute bacterial endarteritis appeared. He was given 3,000,000 units of penicillin and all signs of the infection have been absent for four months. A second patient with patent ductus arteriosus and endarteritis had 225 colonies of *Streptococcus viridans* per cubic centimeter in her blood stream. She received 4,200,000 units with a complete subsidence of all signs of her infection. Following this treatment the ductus was sev-

ered and ligated. The improvement in this young adult's general condition has been extremely satisfactory.

Before patients are treated with penicillin, in vitro tests are carried out with a standard inoculum of the causative organisms to detect the sensitivity of the strains to penicillin. It would appear that more desirable results will be obtained if complete inhibition of growth is obtained with penicillin in concentrations that may be readily attained and maintained in human beings.

### Gonococcic Infections

*Sulfonamide-Resistant Gonorrhea* Sixteen patients, 13 males and three females, having gonorrhea for one to 30 weeks have been treated successfully with penicillin. The total amount of penicillin used varied between 75,000 to 270,000 units, an average of 100,000 units being given in doses of 20,000 units intramuscularly every two to three hours for five doses. One patient, having an acute epididymitis as a complication, was at first thought to have been completely under control following 150,000 units, but he had an exacerbation of epididymitis after physical activity. Another 120,000 units was necessary before the inflammatory process subsided. At the present time, at least, we believe that patients having acute gonorrhea should be hospitalized for therapy with penicillin. Whether short cuts in therapy are possible so that an individual may be treated in a physician's office with smaller doses, or with less frequent injections must be investigated carefully. A potential danger lurks in such a procedure in that patients may be inadequately treated, and strains of gonococci resistant to penicillin may be developed and disseminated. This has been the history of sulfonamide therapy.

*Gonococcic Arthritis* Four patients with gonorrhea and acute arthritis were treated with the total doses of penicillin varying between 100,000 and 707,500 units. Although the gonorrhea was readily controlled, joint tenderness and pain persisted for several days after the conclusion of therapy. This is understandable when one considers the nature of gonococcic arthritis. Within a relatively short period of time after the onset there is an inflammatory reaction of the synovial membrane, and, in some instances, a destruction of joint cartilage. Even following the eradication of viable gonococci this inflammatory reaction subsides slowly. If penicillin could be given parenterally very shortly after the onset of arthritis, and also injected directly into the larger joint spaces when indicated the response might be more dramatic. In our patients, the arthritis was of several days' duration, and the smaller joints of the wrist and feet were involved.

### Genitourinary Tract Infections

Of the 22 patients, 16 constitute a group who have been investigated in cooperation with Dr C D Creevy, Head of the Division of Urology at the University Hospitals. All of them were males with benign prostatic

hypertrophy on whom transurethral resection of the prostate gland was carried out. Relatively small doses of penicillin were administered parenterally shortly before and after operation in an attempt to control a bacteremia or local infection, which are not uncommon complications of this type of surgery. Obviously, conclusions can only be drawn after a larger group is treated.

Four patients having pyelonephritis were treated. They were given 300,000 to 500,000 units of penicillin. Two improved, one recovered completely, and the fourth showed no improvement. Two remaining patients had chronic cystitis. One had temporary improvement, whereas the other failed to improve. All of these patients had infections associated with pyogenic Gram positive cocci. All had received prior sulfonamide therapy. More information is necessary before recommendations can be made concerning the value of penicillin in the treatment of genitourinary tract infections.

#### Miscellaneous Infections

Fifteen patients with miscellaneous infections were treated.

*Peritonitis* There were four patients in this group. All had generalized peritonitis. Two followed perforation of a hollow viscus, one followed a colectomy, and a third resulted from a ruptured appendix. Two recovered. Although one cannot draw conclusions from four cases, one is probably justified in using penicillin in the therapy of peritonitis. Since a mixed type of bacterial flora is usually involved, it may be necessary to supplement penicillin with one of the sulfonamides. It would appear that relatively large doses of penicillin may be necessary.

*Dermatological Lesions* One patient with generalized pemphigus was treated. Hemolytic streptococci, staphylococci and proteus bacilli were isolated from the bullae. No improvement followed the use of large doses of penicillin. A similar result was obtained in a second patient with a chronic dissecting pyoderma. A third patient with severe acne conglobata and a bacteremia due to unidentified Gram positive cocci improved following therapy with penicillin. No new skin lesions developed while the patient was under observation.

*Pneumococcic Bacteremia Without Pneumonia* Two patients were treated. One recovered. A fatal outcome in the second patient was associated with an acute ulcerative endocarditis due to type XXII pneumococci.

*Chronic Burrowing Undermining Ulcer ("Meleney Ulcer")* One patient with a large dissecting lesion of the abdominal wall due to microaerophilic hemolytic streptococci was improved but temporarily following the local and parenteral employment of large doses of penicillin.

*Gas Gangrene* One patient, critically ill with a bacilemia following amputation of a lower extremity for gas gangrene, recovered following the use of large parenteral and local doses of penicillin.

*Actinomycosis* One patient with abdominal and rectal fistulae due to actinomycosis improved considerably following the parenteral administration of two million units of penicillin. However, actinomyces were still recovered from the abdominal drainage at the conclusion of therapy.

*Localized Intra-abdominal Infections* One patient with a postoperative subphrenic abscess improved coincident with the administration of penicillin. A second patient with a postoperative cholangitis and possibly a liver abscess recovered, but penicillin therapy did not appear to be responsible for the favorable outcome.

### Toxic Manifestations

One of the outstanding features in this group of 200 patients was the extremely low incidence of toxic manifestations. While receiving penicillin two individuals had an unexplained rise in temperature which promptly subsided to normal when administration of the drug was discontinued. A third patient developed urticaria after receiving penicillin for one week. Treatment was omitted for 24 hours, and when therapy with the same lot was instituted again urticaria did not appear. Three patients developed a thrombophlebitis at the sites where penicillin had been given intravenously.

### SUMMARY AND CONCLUSIONS

Penicillin is the most effective agent available for the treatment of staphylococcal infections. This also applies to some types of infection due to hemolytic streptococci. There is evidence that some green-producing strains of streptococci and non-hemolytic streptococci are highly resistant to penicillin. It may be anticipated that penicillin will reduce the mortality rate from pneumococcal and staphylococcal meningitis. The drug is also effective in the treatment of meningococcal meningitis, an infection which also responds readily, in most instances, to the sulfonamides. Encouraging therapeutic results have been obtained in infections of the lungs due to pyogenic, Gram positive cocci, and to the pneumococcus. Suppurative empyema and pericarditis may be controlled with penicillin in many cases without the necessity of surgical drainage of the cavities. The anticipation of a more hopeful outlook for patients with subacute bacterial endocarditis because of penicillin must be tempered by a cautious interpretation of clinical data, and treated patients must be checked periodically for evidence of the disease. Penicillin is the drug of choice in the treatment of gonorrhea with and without complications such as arthritis. More data are necessary before ascertaining the value of penicillin in the therapy of genitourinary tract infections other than gonorrhea. Penicillin should be evaluated further in the treatment of generalized peritonitis where preliminary observations appear promising. The drug may be of value in controlling some cases of actinomycosis.

Since penicillin is highly specific in its antibacterial action, it is exceedingly desirable that the physician should obtain all the precise bacteriological data possible before instituting therapy. This is particularly important during the present time when the material available for civilian use is limited. The physician should also remember that the sulfonamides still occupy a respected position in the treatment of infections, particularly in instances in which penicillin is of no benefit.

Although an extraordinary amount of information has accumulated in a relatively short period of time concerning penicillin, there remain some unsolved clinical problems that will require further clinical experience before their solution is at hand. One pertains to the optimal doses of penicillin to be used in a specific infection. Because the supply of the drug continues to be limited considerable stress has been placed on the minimal requirements. Although the majority of patients may respond favorably to the minimal doses set up, a continuance of such a philosophy is fraught with two potential dangers. First, an infection may be controlled but not eradicated. Second, there is the possibility that penicillin-resistant strains may develop and may be disseminated. In our own experience, two patients with staphylococcic sepsis were treated with what were believed to be adequate doses of penicillin but the infections were not completely brought under control. After the conclusion of therapy, staphylococci isolated from local lesions were found to be much more resistant *in vitro* than the parent strains obtained before therapy was instituted. There is a possibility that the use of inadequate doses of penicillin in patients with gonorrhea may cause the development of strains of gonococcus resistant to penicillin. Finally, further investigations should determine whether penicillin given concurrently with the sulfonamides may yield better results in the treatment of certain types of infections.

# SEPTIC PULMONARY INFARCTION; REPORT OF 8 CASES

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THE clinical features of pulmonary infarction in general are well known and have been a popular topic in recent literature. On the other hand, the manifestations of septic pulmonary infarction in particular have received comparatively little attention except for occasional case reports. It is the purpose of this report to present the diagnostic aspects of this type of infarction and to emphasize that prompt surgical treatment may be of great importance in its prevention. The cases reported here have been selected partly with a view to calling attention to some of the less common sources for pulmonary infarcts.

In any case of septicemia caused by a pyogenic organism, abscesses may occur in the lungs as well as elsewhere. In a sense, these are embolic abscesses, but we have not included cases of this type in this discussion. Rather, we have been interested in the situation in which a septic thrombus in the peripheral veins or in the right side of the heart becomes dislodged, enters the pulmonary circulation, and causes infarction. The infarcted area in this event is infected from the start as opposed to the occasional case of a bland infarct which becomes secondarily infected by contamination through the bronchial tree<sup>1</sup>. Some idea of the comparative rarity of septic pulmonary infarction can be gained from the report of Hedblom<sup>2</sup> to the effect that in 528 collected cases of pulmonary abscess only 3.9 per cent were of certain or probable embolic origin.

## PULMONARY INFARCTION FOLLOWING PHARYNGEAL INFECTION

### CASE REPORTS

*Case 1* L. J., a 39 year old negro, was admitted to the hospital complaining of severe sore throat of three weeks' duration. He was semicomatose and unwilling to open his mouth because of pain. The patient was acutely ill, groaning and stuporous. The temperature was 102° F, pulse 110, and respirations 22. The sclerae were moderately icteric. There was marked swelling of the left anterior faucial pillar and both tonsils were enlarged. Below the angle of the left mandible there was a fixed, tender, indurated mass. The submaxillary lymph nodes on the left were palpable. Fine moist râles were present over the lower part of the right hemithorax posteriorly. There was marked tenderness and moderate rigidity over the right upper quadrant of the abdomen.

The urine contained a trace of albumin and was positive for bilirubin. The red cell count was 3,600,000, the white cell count 14,100 with 73 per cent neutrophils, 12

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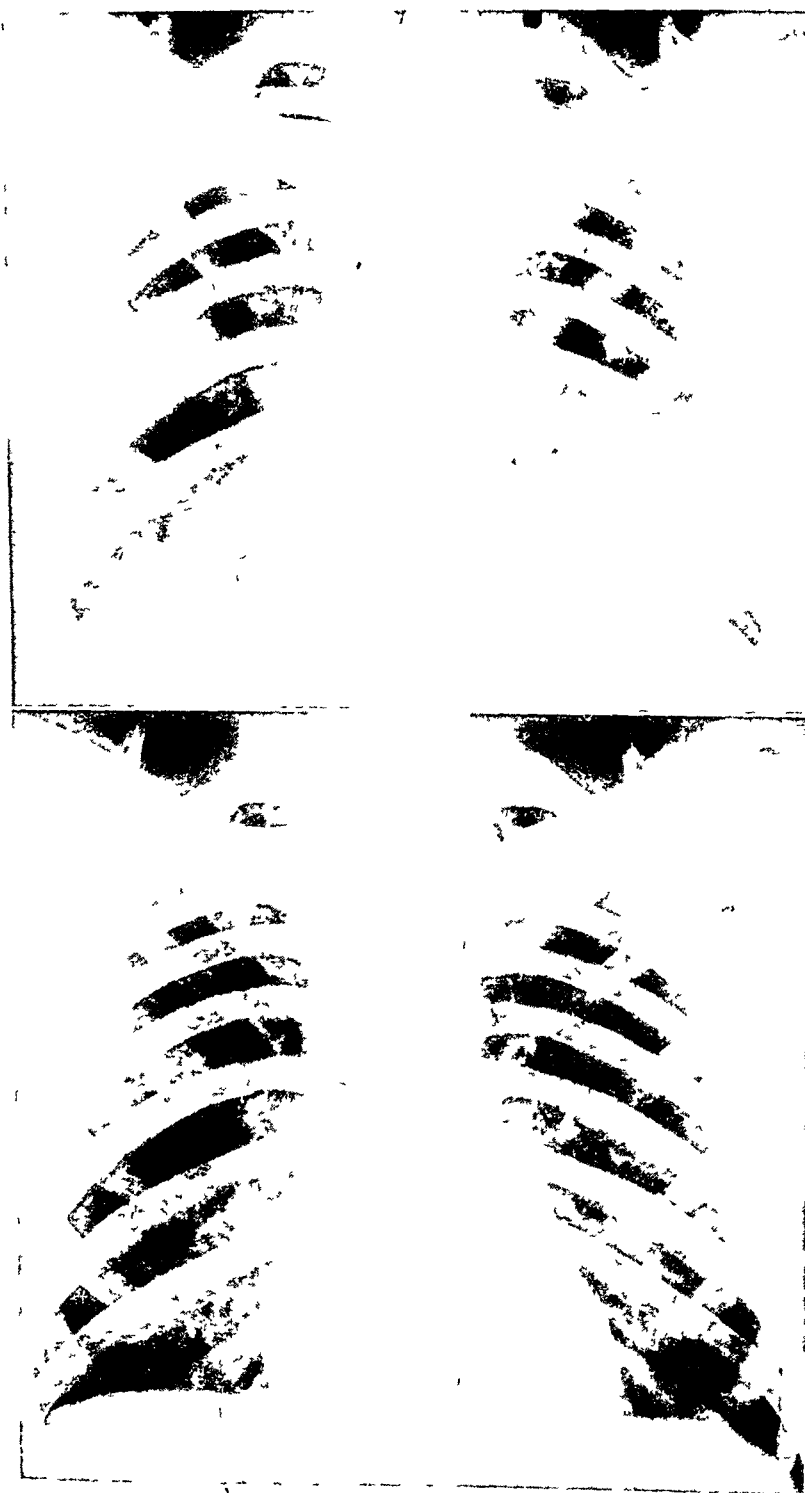


FIG 1 (*above*) (Case 1) Rounded areas of increased density in lower halves of both lung fields suggesting pulmonary infarcts

FIG 2 (*below*) (Case 1) Clearing of infarcts with residual fibrosis



per cent bands and 15 per cent lymphocytes. A blood smear was negative for sickling. The blood Kahn reaction was negative, blood urea nitrogen 60 mg per 100 c.c., blood creatinine 3 mg, icterus index 96. The agglutination tests for spirochetal jaundice were negative. Throat culture yielded *Staphylococcus aureus*, and blood cultures repeatedly showed *Staphylococcus albus*. A portable roentgenogram of the chest showed small areas of opacity in the lower halves of both lungs.

Sulfadiazine therapy was instituted, and the blood levels were kept between 6 and 10 mg per 100 c.c. The inflammation of the throat subsided rapidly during the first two weeks of hospitalization, but the patient continued to be critically ill, febrile, and icteric. He had developed a cough which was productive of purulent and bloody sputum. A roentgenogram of the chest at this time showed scattered areas of increased density in the lower halves of both lung fields. Their appearance suggested multiple pulmonary infarcts (figure 1).

During the third and fourth weeks there was general improvement, but the cough continued, and roentgen-ray examination of the chest showed no change until the end of the fourth week when rarefaction was discernible in some of the areas of infarction. Blood cultures were still positive for *Staphylococcus albus* and slight jaundice remained.

His cough subsided considerably during the fifth week, and the sputum was mucoid and no longer bloody. He had occasional episodes of chest pain which was intensified by coughing and deep breathing. The mass at the angle of the left mandible was smaller and no longer tender. After the fifth week the temperature was normal except for an occasional rise to 100° F. Gradually the cough and expectoration disappeared, and the swelling at the angle of the jaw became barely palpable. Blood cultures were negative after the sixth week. Roentgenograms of the chest showed steady regression in the areas of infarction, but a cavity 2 cm. in diameter appeared at the left base. The patient felt well at the time this was noted, however, and was gaining weight rapidly. At the time of his discharge from the hospital, after 82 days, the roentgenogram was negative except for residual fibrosis in some of the previously described areas of infarction (figure 2).

*Case 2.* L. S., a 24 year old negro, entered the hospital complaining of a sore throat, fever and chest pain. Four weeks prior to admission he developed a severe sore throat accompanied by fever and malaise. The following week he noticed the onset of a cough which was productive of blood-streaked sputum on several occasions. He also had pain in the front of his chest on the left side. This pain was intensified by coughing and deep inspiration. His sore throat continued but was less intense. During the next two weeks his cough, fever, and chest pain became worse.

The patient appeared acutely ill and jaundiced. His temperature was 101.5° F, pulse 110, and respirations 28. Both tonsils were enlarged and pus could be expressed from the follicles of the left. The left submaxillary lymph nodes were enlarged and tender. Motion of the left hemithorax was restricted, and there was a friction rub in the left axilla.

The urine was normal. The red blood cell count was 3,000,000, the white blood cell count 18,800. The icterus index was 56. Blood cultures were negative, and there were no blood agglutinins against *Leptospira icterohaemorrhagiae* and *Leptospira canicola*.

The patient received no specific therapy. His fever continued for the first eight days. At the end of this period he appeared much improved. His cough was less, and his icterus had decreased. His throat was no longer painful. A roentgenogram of the chest at this time showed round areas of opacity with rarefaction in the central part of one of these areas (figure 3). Convalescence was uneventful until the seventeenth hospital day, when a tender, movable mass was felt medial to the lower third of the left sternocleidomastoid muscle. At this time there was again mild fever.

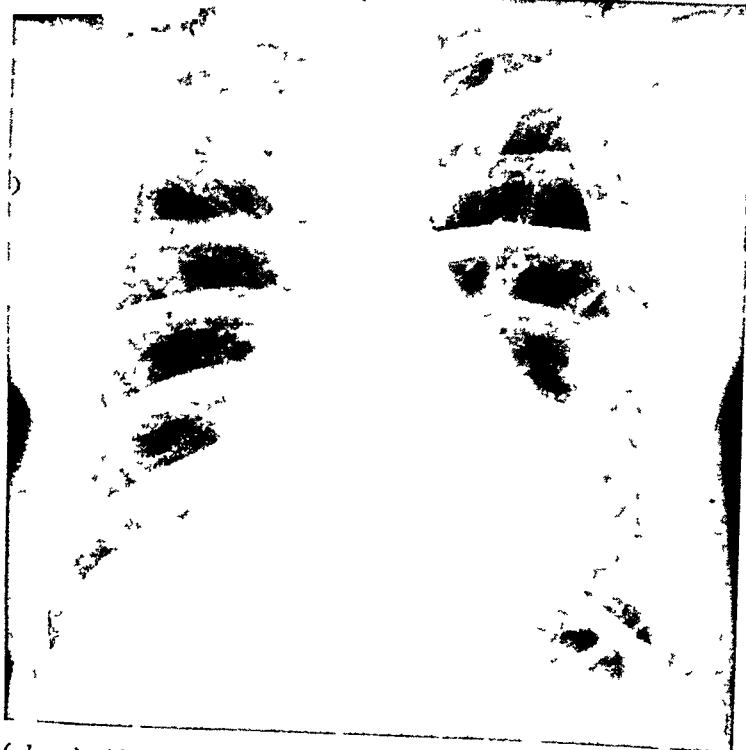
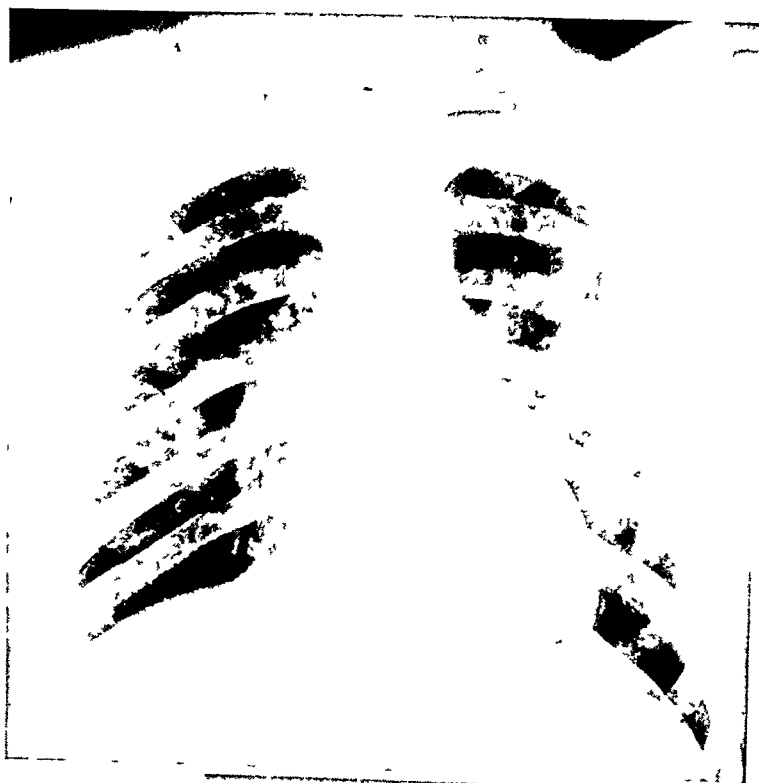


FIG 3 (above) (Case 2) Rounded areas of opacity with central rarefaction in both lungs

FIG 4 (below) (Case 4) Areas of increased density in lower half of left lung

for a few days. The mass was treated by roentgen-ray irradiation and was observed to shrink considerably. Surgical exploration of the mass disclosed a small collection of pus and a thrombosed internal jugular vein.

The patient continued to remain symptom-free until his discharge on the thirty-ninth hospital day. His roentgenograms showed gradual complete clearing of the pulmonary lesions except for residual fibrosis and pleural thickening in the involved areas.

*Case 3* E. G., a 28 year old white woman, was admitted to the Georgetown University Hospital on December 4, 1940. Her illness had begun six days before admission with sore throat, chilliness, prostration, and fever. There had first been typical findings of follicular tonsillitis, and two days later a peritonsillar abscess had developed on the left side. During an episode of vomiting the abscess had ruptured and had been draining continuously since. Fever and severe prostration had persisted. The day of entrance to the hospital she had developed pain in the left flank, aggravated by breathing and by movement.

On examination at the time of admission the patient looked acutely and seriously ill. The respirations were noisy and rapid and accompanied by dilation of the alae nasae. The blood pressure was 118 mm Hg systolic and 72 mm diastolic, pulse 128, temperature 100° F. There was great enlargement in the left tonsil area where there was a ragged hole from which pus was draining. The right tonsil was inflamed but not much swollen. The cervical lymph nodes were not enlarged but there was exquisite tenderness of the left side of the neck. The heart and lungs were negative. When the patient's body was raised she complained of severe pain in the left flank. The abdomen was tense and there was tenderness in the left flank and at the umbilicus.

The urine contained a moderate amount of albumin but was otherwise normal. The erythrocyte count was 4.46 million, the leukocyte count 16,600 with 73 per cent segmented neutrophils, 12 per cent band forms, and 15 per cent lymphocytes. The blood culture yielded no growth. *Streptococcus viridans* and *Staphylococcus aureus* were obtained on culture of the pus draining from the left tonsil.

Sulfapyridine was administered from the start, and the blood level was maintained above 10 mg. per 100 c.c. The urinary and blood findings altered little from day to day, except that mild anemia developed by the fourth hospital day and persisted in spite of transfusions of 500 c.c. each of whole blood given every other day. On the second hospital day it was noted that the patient was coughing frequently and unproductively. She still looked quite ill but she was having no pain and the neck was less tender. Moderate fever, tachycardia, and polypnea persisted, and slight cyanosis was noted. There was dullness at both lung bases and bronchial breathing over the right. From this day on she became progressively worse. The temperature and pulse fluctuated widely, and the respirations were variably shallow and continuously rapid. Râles appeared over both lower lobes in back, and a portable roentgen-ray film of the chest showed scattered opacities throughout the right lung and opacity of the left lung field from the second rib down. The roentgenologic diagnosis was bilateral generalized bronchopneumonia.

On the eighth hospital day the patient coughed up a plug of material from the left side of her throat, after which the peritonsillar abscess drained more profusely than ever. The next day she complained of severe pain in the left side of the neck, and by the following day there was extensive cellulitis. The area was treated with roentgen-ray irradiation, and within a few days it became fluctuant. It was then incised, using local anesthesia, and a large amount of foul pus escaped. Soon thereafter there were indications of peripheral circulatory collapse which became steadily worse. The patient died on the thirteenth hospital day.

Necropsy demonstrated that the abscess in the neck extended down to the inferior

margin of the thyroid cartilage in the pretracheal fascia. The left internal jugular vein was thrombosed. There was bilateral empyema. The lower lobe of the left lung was completely atelectatic. The left upper lobe and the right middle and lower lobes contained innumerable discrete abscesses, varying in size from 0.25 to 1 cm in diameter. Almost all of the abscesses were located in the periphery of the lungs.

### DISCUSSION

These three cases represent examples of septicemia and pulmonary infarction accompanying pharyngeal infection. The pathogenesis of this type of septicemia has been summarized in articles by Hall<sup>3</sup> and Boharas<sup>4</sup>. These authors describe several modes of development of the process. It may follow almost any type of infection in or around the tonsil. In the cases that we have reported there was obvious acute tonsillitis, and in two of them a peritonsillar abscess was present. In some cases the initial focus of infection may remain unknown, and the condition may be recognized by signs of thrombophlebitis of the internal jugular vein. Hall<sup>3</sup> has reported that the picture of septicemia, with or without pulmonary involvement, may occur days or even weeks after the manifestations of local involvement in the pharynx have subsided. This latter type of case perhaps needs special emphasis because of the comparative obscurity of the focus of the disease.

An infection of the tonsil or peritonsillar area may reach the systemic circulation by producing thrombophlebitis of the tonsillar and peritonsillar veins. This thrombotic process may then extend into the internal jugular vein. Although this mode of involvement is stated to be rather less common, it appears to have been the one operating in Cases 1 and 2. More commonly thrombophlebitis of the internal jugular results from direct extension of the inflammatory process from the pharynx by way of the parapharyngeal space as exemplified in Case 3. The parapharyngeal or pharyngomaxillary space is posterior and lateral to the tonsil and separated from it only by the superior constrictor pharyngeus muscle. It must be understood that similar involvement of the internal jugular vein may result from infections in other locations than the tonsil, provided the area of infection is in contact with the vein or is drained by veins which empty into the internal jugular.

The local manifestations of pharyngeal infection complicated by septicemia are variable. Case 1 illustrates the fact that there may be no local signs except the ones ordinarily encountered in cases of uncomplicated pharyngeal inflammation. Here the clue to the diagnosis was to be found entirely in the systemic manifestations. It is only when the parapharyngeal space is the site of a phlegmonous inflammation that local signs may be prominent. With involvement of the parapharyngeal space there may be swelling and induration over the parotid gland and below the angle of the jaw and peritonsillar swelling and induration with few or no signs of pharyngitis. With extension of thrombophlebitis into the internal jugular vein there may be tenderness and swelling along the anterior border of the

sternocleidomastoid muscle. Of all the local signs tenderness at the angle of the jaw is most frequently noted. In one of our cases (Case 2) there was frank evidence of periphlebitis of the internal jugular vein, indicated by the considerable swelling, tenderness, and induration along the sternocleidomastoid muscle. It is interesting that the phenomena appeared in Case 2 some days after all other local and systemic manifestations of disease had subsided. In Case 3 there was persisting evidence of a peritonsillar abscess and tenderness at the angle of the jaw until about 48 hours before death, at which time the rapidly developing cellulitis of the neck probably resulted from extension of an infection from the parapharyngeal space.

The general symptoms encountered in these cases are those that might be expected in any similar septicemia. Jaundice was present in two of our cases and, as is true in most cases of septicemia, was of the hepatocellular type. In spite of the obvious clinical evidence of blood stream infection in all cases, blood cultures were negative in all but Case 1 in which the *Staphylococcus albus* was obtained. The general experience with the disease under discussion indicates that blood cultures are positive in only about half the cases.

The pulmonary lesions in the three cases reported above were a prominent feature. Although the systemic effects of the local disease were obvious in all cases, the appearance of the pulmonary lesions was the first clear indication of the need to search for a focus of thrombophlebitis. This fact was not accurately appraised during life in Case 3, mainly because the roentgen-ray appearance of the pulmonary disease was interpreted as bronchopneumonia. In Cases 1 and 2, the chest films were typical of pulmonary infarction, showing well defined, scattered areas of increased density. Recognition of the septic nature of the infarcts was facilitated, as serial films demonstrated the development of a radiolucent center and at times a fluid level in some of the previously homogeneous shadows (figures 1 and 3). This kind of cavitation is not peculiar to septic infarcts, however, for lung abscesses may develop in cases of bland infarcts as a result of infection extending from the bronchial tree.<sup>1</sup> In Case 3 bilateral empyema was discovered at autopsy. This complication is not unusual in cases of embolic lung abscesses, since the peripheral location of the lesions favors involvement of the pleura by the infecting organism. In addition to pulmonary abscesses, there may occasionally be other metastatic suppurative lesions in almost any location. Other serious but less common complications have been reported<sup>3, 4</sup> but hardly require enumeration here.

The serious nature of this type of sepsis can be emphasized by the fact that the mortality is high in untreated cases. Formerly, it was agreed that the only effective form of treatment was surgical, consisting of the provision of adequate drainage for any accumulated pus, with or without ligation of the internal jugular vein. Without this form of treatment the mortality was almost 100 per cent. It may be that the use of sulfonamides and penicillin will materially reduce the mortality rate in cases in which surgical treatment

is delayed or not employed. Our Cases 1 and 2 confirm this impression. However, it is not to be understood that we condone a program of treatment which does not include surgical measures, particularly ligation of the internal jugular vein. In summary, the treatment should consist of controlling the septic focus by chemotherapy and surgical drainage if necessary. Isolation of the septic focus from the circulation is accomplished by means of ligation of the internal jugular vein. When the vein is thrombosed, ligation should be performed below the thrombus to prevent embolism or further propagation in this direction and above the thrombus to prevent retrograde extension toward the brain. The treatment of metastatic abscesses requires chemotherapy and surgical drainage where practicable. The pulmonary lesions are usually not susceptible of surgical treatment because they are multiple. In the rare case of a solitary metastatic lung abscess operation may be necessary.

#### PULMONARY INFARCTION COMPLICATING BACILLIAL ENDOCARDITIS

##### CASE REPORTS \*

*Case 4* C S, a 38 year old negro, had begun taking heroin three months before admission to the hospital. The drug had been suggested by a friend as a means for relieving cough, anorexia, night sweats, and vague chest pain. The heroin had been administered daily and intravenously without use of sterile technic. The cough continued, and he observed increasing fatigue and the loss of 18 pounds during the three month period. Because of these symptoms and the onset of fever and dyspnea he entered the hospital. A roentgenogram of the chest taken one week before admission had been reported as negative.

On examination the patient was acutely ill and dyspneic. The temperature was 102.5° F, pulse 125, and respirations 32. The only other positive findings included diminished breath sounds and subcrepitant râles over the left lower lobe posteriorly. The veins in the antecubital fossae and forearms were indurated as the result of intravenous administration of heroin. The urine was normal. The white blood cell count was 13,000 with 90 per cent neutrophils and 10 per cent lymphocytes. The red blood cell count was 3,800,000. Roentgen-ray examination of the chest showed areas of increased density in the lower half of the left lung (figure 4). The heart showed a slight increase in its transverse diameter.

A blood culture taken on the third day was reported to show *Staphylococcus albus*. The patient was given sulfamerazine, and adequate levels were obtained. Repeated blood cultures showed *Staphylococcus aureus*, which was coagulase positive. A roentgen-ray film taken on the seventh hospital day revealed discrete areas of soft infiltration containing radiolucent centers scattered throughout both lungs (figure 5).

The patient continued to be extremely ill. He remained dyspneic and his temperature varied between 100° and 105° F. He coughed up blood-tinged sputum on several occasions. The white blood cell count ranged between 18,000 and 21,000. Frequent examinations of the heart failed to reveal any murmurs. A roentgen-ray film on the thirteenth day showed further cavitation in the many areas of infiltration scattered throughout both lungs. He died on the fourteenth hospital day.

Necropsy showed large friable vegetations on the tricuspid valve. Innumerable abscesses were present in both lungs, varying in size from 3 mm to 2 cm in diameter. Cultures obtained from the vegetations and from the lung abscesses were positive for *Staphylococcus aureus*.

\* The following three cases were included in a previous report.

*Case 5* O B, a 25 year old negress, gave a rather vague history, owing to the severity of her illness. Her health had been good until three weeks before admission when she had developed fever, vomiting, and symptoms of an upper respiratory infection. For one week before admission she had had a sore throat and cough.

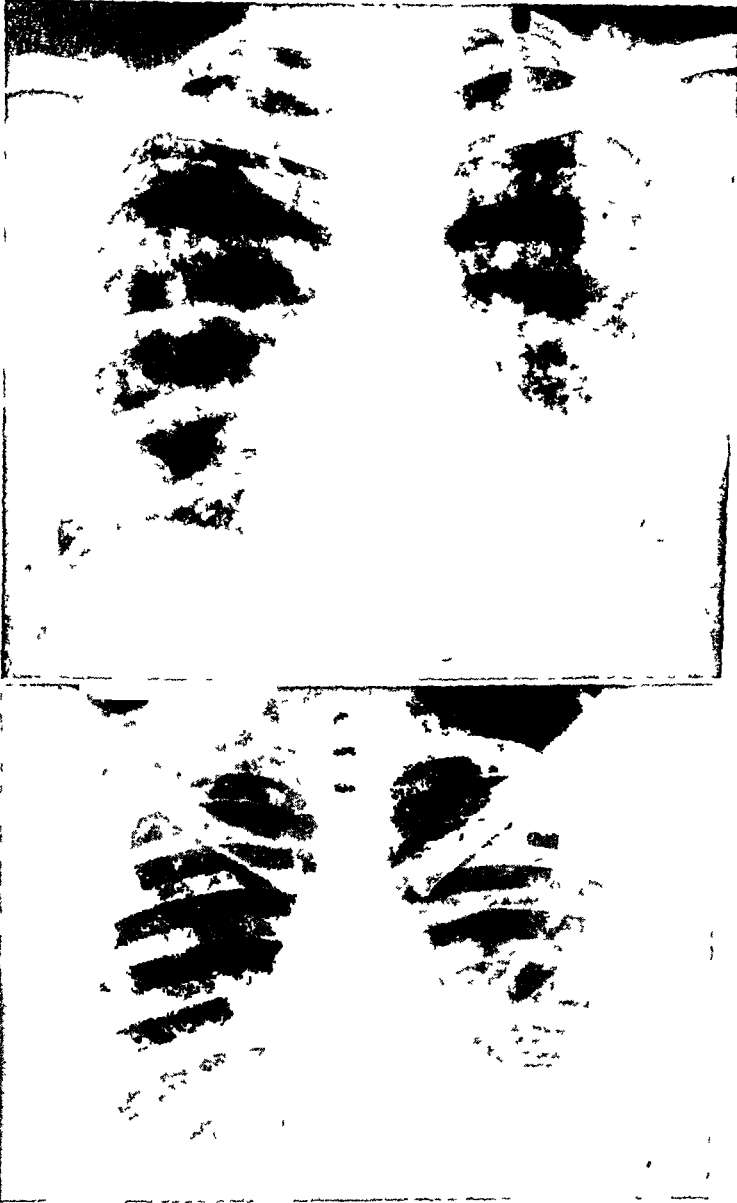


FIG 5 (above) (Case 4) Multiple infarcts showing cavitation due to abscess formation  
 FIG 6 (below) (Case 5) Scattered small pulmonary infarcts

Six days prior to entry she had rubbed her face and body with alcohol, then camphorated oil to alleviate a headache. The next day she broke out in welts and the following day began to peel. She stated that she was about six months pregnant.

The patient was well developed, slightly obese, stuporous, and acutely ill. Her

temperature was 102.5° F, pulse 130, respiratory rate 48 to 60. Her face was swollen and there was extensive patchy exfoliation over her arms and chest, leaving cracked and bleeding areas. There were several flattened bullous lesions on the arms. There were decreased resonance at the right lung base, increased breath sounds over both lung bases and infraclavicular areas, and fine moist râles in both axillae and over the right base posteriorly. The heart size was normal and there was a short soft systolic murmur to the left of the sternum. There was gallop rhythm. The uterus reached the umbilicus and fetal heart sounds were heard. Extensive raw areas were seen around the vulva.

A roentgen-ray film of the chest showed circumscribed areas of opacity scattered throughout both lung fields, suggesting pulmonary infarcts (figure 6). The urine contained a moderate amount of albumin. There was moderately severe anemia, which persisted throughout the course of the illness in spite of frequent blood transfusions. The leukocyte count was high, ranging from 12,300 to 20,500. Blood cultures were repeatedly positive for *Staphylococcus aureus*.

Sulfamerazine was first administered for 48 hours. The identity of the organism causing septicemia then being learned, penicillin was substituted. The day after penicillin was started the patient seemed slightly better. Her breathing was less labored, and she was slightly more alert. Fever and tachycardia persisted, however. On the next day pulsus alternans was detected, although the patient continued to appear somewhat improved. The skin lesions showed considerable healing. This improvement was transient, for on the sixth day she became extremely stuporous. Her respirations became more labored and the pulse considerably weaker. This downward course continued, and she died on the ninth hospital day.

It was subsequently learned from the patient's husband that she was addicted to the use of heroin. This drug was administered intravenously without aseptic precautions.

Necropsy revealed acute bacterial endocarditis of the tricuspid valve with multiple septic pulmonary infarcts which had progressed to form pulmonary abscesses. The six months fetus appeared to have been dead for several days.

*Case 6* F N, a 28 year old negress, had been having daily chills and fever for 10 days before admission to the hospital. Six days before admission she noted a sudden, piercing pain in the upper half of the left hemithorax, intensified by deep inspiration. A nonproductive cough began that day. She was seen by a physician who informed her that she had pleurisy and prescribed sulfathiazole. On the following day her cough became productive of a thick brown sputum. The cough and pain had continued.

The patient admitted having taken heroin intravenously for the preceding four months. The syringe and needle used for this procedure had not been sterilized. Her last injection had been given three weeks previously. She had lost 50 pounds during the period of her narcotic habit.

The patient was emaciated, dyspneic and complaining of chest pain. The temperature was 102.8° F, pulse 110, respirations 32, and blood pressure 100 mm Hg systolic and 75 mm diastolic. Both forearms were scarred along the course of the veins. There were bronchovesicular breathing and moist râles over the left upper lobe posteriorly. There was a soft systolic murmur heard over the mitral area.

The white blood cell count was 6,400 with 75 per cent neutrophils and 25 per cent lymphocytes. Urinalysis showed a trace of albumin. Smears for malaria were negative. Roentgen-ray examination of the chest showed small areas of infiltration in the left upper lobe (figure 7). Repeated blood cultures were positive for *Staphylococcus aureus*. The patient was given sulfamerazine and supportive therapy. Because of the likelihood of acute bacterial endocarditis and pulmonary infarction, penicillin was not administered.



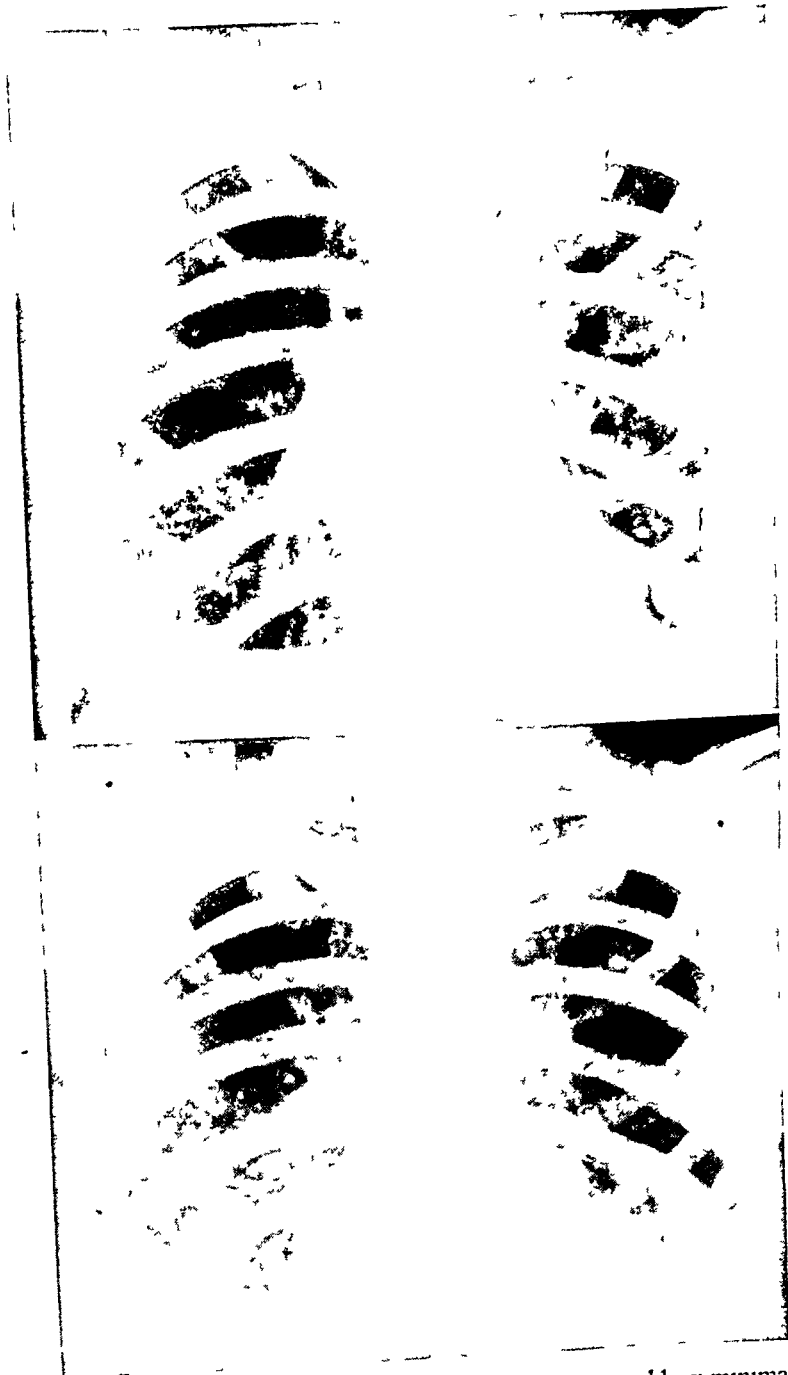


FIG 7 (above) (Case 6) Infiltration in left upper lobe resembling minimal tuberculosis  
FIG 8 (below) (Case 6) Wedge-shaped infarct in lower part of right upper lobe, clearing of left upper lobe

There was no great change in the patient's condition during the following week except that the pain in her chest was less severe. On the seventh hospital day she expectorated blood-streaked sputum. This expectoration continued for the next few days at which time a roentgen-ray film of the chest showed clearing of the areas of infiltration in the left upper lobe and a wedge-shaped shadow of increased density in the lower lateral portion of the right upper lobe (figure 8). The remainder of the patient's course was rapidly downward. She was confused and her temperature varied between 100° and 105° F, with frequently recurring chills. She had repeated small hemoptyses. Physical and roentgen-ray examination disclosed many new areas of infarction in both lungs. No new heart murmurs were heard. The blood cultures continued to be positive for *Staphylococcus aureus*, and the red cell count showed a steady decline, although no evidence of jaundice appeared. She died on the thirty-first hospital day.

At necropsy there was acute bacterial endocarditis of the tricuspid valve. There were many pulmonary infarcts all of which had undergone abscess formation. There was empyema of the right pleural cavity. The spleen was moderately enlarged.

### DISCUSSION

These three cases of acute bacterial endocarditis are almost identical in every respect. All three patients were young negro adults who were addicted to the use of heroin intravenously. They developed *Staphylococcus aureus* septicemia, presumably owing either to contamination of the heroin or to lack of aseptic technic during injection of the drug. Acute bacterial endocarditis involving the tricuspid valve ensued in each case. In none of the cases was there evidence of preexisting heart disease. From the focus in the right side of the heart septic emboli were carried to the lungs, resulting in infected infarcts and abscesses (figure 5). In Cases 4 and 6 the initial roentgenogram resembled minimal pulmonary tuberculosis (figures 4 and 7). However, in both cases the severity of the clinical picture was incompatible with this diagnosis. The correct clinical diagnosis was made during life in each case, when it was apparent that there was no other probable focus for the septic pulmonary infarcts than the right side of the heart. The absence of a diastolic murmur was presumptive evidence that the endocarditis involved the tricuspid and not the pulmonic valve. Treatment in all cases consisted of the administration of one of the sulfonamides and supportive therapy. In Case 5 penicillin was also used. None of the patients recovered.

### PULMONARY INFARCTION FOLLOWING PELVIC THROMBOPHLEBITIS

#### CASE REPORTS

*Case 7* N W, a 37 year old negro multipara, had been pregnant about three months when she developed a severe chill, followed by fever. Two days later there were cramps in the lower part of the abdomen and vaginal bleeding began. A few days afterward, on June 6, 1943, she was admitted to the hospital.

On examination the patient did not appear acutely ill. Her temperature was 99° F, pulse 130, respirations 20, and blood pressure 120 mm Hg systolic and 80 mm diastolic. Her breasts were soft and contained colostrum. The heart and lungs were

normal The uterus was twice normal size and a scanty, foul, reddish brown vaginal discharge was present The urine showed one plus albumin and occasional red and white blood cells The red blood cell count was 3,210,000 and the white blood cell count was 13,000 The Kahn reaction was negative

Sulfathiazole was started on admission During the next two days the vaginal bleeding increased and the temperature reached 103° F The patient now complained of pain over the lower abdomen and there was tenderness in this area The white blood cell count rose to 26,500 During the ensuing two weeks the temperature curve was of a septic character and varied between 99° and 105° F On the twelfth hospital day there was sudden pain over the front of the chest on the right side, but roentgen-ray examination of the chest was negative Blood cultures also were negative

By July 5, one month after admission, the course was still septic There was tenderness in the left adnexal region with some fixation and fullness and a profuse foul, yellow, vaginal discharge was present On July 15 a roentgen-ray film of the chest showed diffuse mottling at the right base and a week later another film showed infarcts scattered throughout both lungs At this time sulfamerazine was substituted for sulfathiazole Blood transfusions were given frequently There was now a cough which was productive of frothy, and occasionally blood-streaked sputum, but the patient appeared less ill than before However, fever and leukocytosis persisted

By August 5 the pelvic mass had decreased in size The patient felt much improved and her temperature had been normal for 48 hours She continued to be afebrile and to have a slight cough for the next week At the end of this period a roentgen-ray film of the chest showed many cavities within the areas of infarction (figure 9) From this time until her discharge there was constant improvement The roentgenograms of the chest showed many fluid-containing cavities which later disappeared to be replaced by strands of fibrous tissue (figure 10) The pelvic mass disappeared except for some adnexal thickening

*Case 8* L B, a 24 year old negress, was admitted to the hospital complaining of intermittent, lower abdominal pain and vaginal bleeding of four days' duration These symptoms had begun at a time when her menstrual period was about 10 days overdue The day before admission she had observed a foul-smelling piece of tissue accompanying her vaginal flow

On examination the patient did not appear ill The temperature was 99° F, pulse 95, respirations 22, and blood pressure 110 mm Hg systolic and 70 mm diastolic Protruding from the vagina was a large piece of necrotic placenta The uterus was about three times normal size The urinalysis was normal, white blood cell count 14,500, red blood cell count 4,300,000

On the second hospital day she had a chill and her temperature rose to 101.5° F There was no change in her physical examination A blood culture taken at this time was negative Sulfathiazole was started and adequate levels obtained From then on her course was septic The erythrocyte count declined and the leukocyte count was persistently high

On the eighth hospital day tenderness was noted above the inguinal ligament on the right side On rectal examination there was a hard, exquisitely tender mass which extended into the cul-de-sac from the right adnexal region The impression at this time was pelvic cellulitis and pelvic thrombophlebitis On the twelfth hospital day she developed a troublesome cough which was productive of slightly blood-tinged sputum Moist râles were heard over the lower halves of both lungs The impression was pulmonary infarction originating from a right pelvic thrombophlebitis Roentgen-ray examination of the chest at this time showed diffuse mottling and many cavities in the upper halves of both lungs A film made seven days later showed progression in the amount of infiltration and cavitation, and many of the cavities

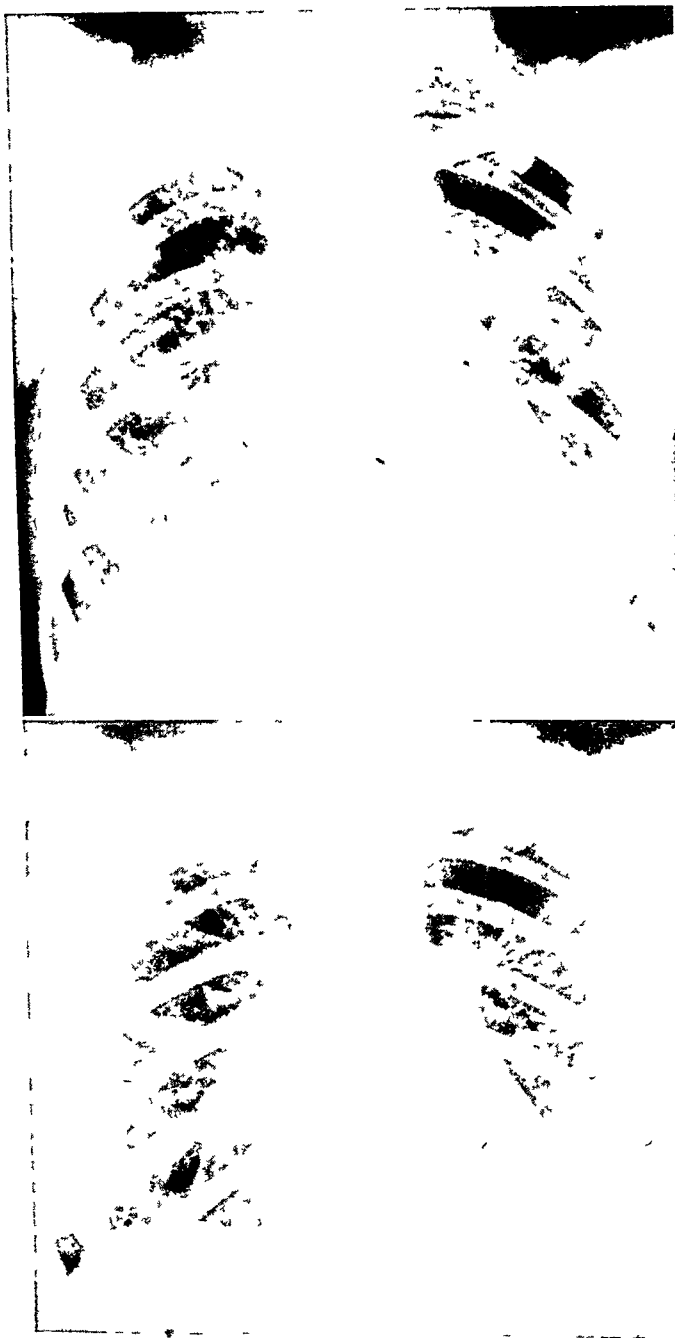


FIG 9 (above) (Case 7) Multiple infarcts with cavitation

FIG 10 (below) (Case 7) Clearing of infarcts with residual strands of fibrosis

contained fluid levels (figure 11) The remainder of the course was steadily downward, and she died on the twenty-fourth hospital day

At necropsy there was an indurated inflammatory mass at the right of the cervix In the center of this mass there were many dilated pelvic veins containing necrotic thrombi and pus Thrombi were found in both common iliac veins and in the lower part of the inferior vena cava The lungs contained many abscesses located at the



FIG 11 (Case 8) Multiple infarcts with cavities, some showing fluid levels

periphery There was purulent pleuritis on the left side where one of the abscesses had ruptured

#### DISCUSSION

These were cases of pelvic infection with secondary thrombophlebitis originating in the pelvic veins and extending variably . It is probable that the danger of embolism increases proportionally to the degree of extension of the process, particularly when the venous thrombosis reaches the common iliac vein In both cases the pelvic infection followed abortion There was a very hectic clinical course, which in each instance had its inception some days before the development of pulmonary infarction In spite of the fact that there were clinical manifestations of septicemia, blood cultures were uniformly negative

The roentgen-ray appearance of the pulmonary lesions varied In the first chest film of Case 7 there was diffuse mottling which resembled the

picture of bronchopneumonia. In subsequent films there was the characteristic appearance of infarcts, later showing cavitation with and without fluid levels (figure 9). In Case 8 the first chest film was made at a time when the pulmonary infarcts had already undergone cavitation.

The treatment was similar in both cases, consisting of the administration of adequate doses of one of the sulfonamides, frequent blood transfusions, and other supportive treatment. One of the patients died, the other recovered after a prolonged, stormy course. The high mortality associated with this kind of illness emphasizes the need for improvement in therapy. Certainly, venous ligation performed with a view to isolating the thrombosed pelvic veins has much to recommend it in selected cases. In cases of severe pelvic infection a decision to ligate the common iliac vein or even the inferior vena cava is difficult to make, because the diagnosis of pelvic vein thrombosis usually must await the occurrence of pulmonary infarction or the development of edema of one or both lower extremities, indicating extension of the thrombotic process.

### SUMMARY

The eight cases presented here are examples of septic pulmonary embolism. They illustrate several of the sources from which such emboli may originate. Other sources, of course, can be called readily to mind, particularly lateral sinus thrombosis and septic thrombophlebitis of the peripheral veins. In three of the cases the failure to find any source for pulmonary emboli in the venous system permitted the diagnosis of acute bacterial endocarditis of the right side of the heart. In every case the pulmonary lesions were the first clear indication that a septic focus existed. This experience is not restricted to cases of septic pulmonary infarction. Pulmonary infarction in general is often the first obvious announcement of the presence of a thrombotic process in the veins.

The roentgen-ray appearance of the pulmonary lesions is variable. Bronchopneumonia may be simulated, or there may be a more or less typical rounded or wedge-shaped peripheral opacity (figures 1 and 8). Some of the septic pulmonary infarcts rapidly develop central rarefaction, indicating abscess formation. The presence of a fluid level signifies that the abscess communicates with a bronchus. It is only in this event that there is likely to be purulent sputum. There is often an area of pneumonitis surrounding the septic infarct. The infarct may enlarge peripherally, because of increasing tissue destruction, and cause extensive pleuritis or even empyema. The lesion may resolve spontaneously and leave no trace or an area of pleural thickening or a strand of pulmonary fibrosis (figures 2 and 10). It is interesting that some of these pulmonary lesions that obviously have undergone abscess formation may resolve so completely without evident drainage. The type of pulmonary lesions described in these cases may occasionally be due to septicemia alone, but in this event there are often abscesses in the

other organs, whereas there were no metastatic abscesses in the cases reported here except in the lungs

The systemic manifestations in all these cases are essentially those of septicemia. The blood cultures may or may not be positive.

There is no specific treatment for multiple septic pulmonary infarcts. The important consideration is isolation of the source of the emboli when this can be accomplished by venous ligation. The use of antibacterial agents and supportive therapy is indicated in all cases. To date there are no adequate measures for dealing with cases of septic pulmonary infarction resulting from acute bacterial endocarditis, with the possible exception of the somewhat encouraging results from the use of penicillin.

### CONCLUSIONS

1 Eight cases of septic pulmonary infarction have been presented. The sources of the pulmonary lesions were a septic process in the pharynx, acute bacterial endocarditis of the tricuspid valve, and pelvic thrombophlebitis complicating pelvic infection.

2 The presence of septic pulmonary infarcts may be the first indication of the need to search for a septic thrombotic process in the venous system.

3 In appropriate cases it is important to ligate the veins through which the infected emboli enter the blood stream.

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# MENINGOCOCCIC MENINGITIS · REPORT ON 165 CASES

By ANDREW H MEYER, *Oakland, California*

DURING the period from July 1942 through May 1944, 165 cases of meningococcic meningitis were seen at the Highland-Alameda County Hospital. As this is a relatively large series, it was decided to report the group, especially since the mortality in the proved cases was 4 per cent.

Of these 165 cases, the spinal fluid showed meningococci on direct smear in 120 instances and positive cultures in an additional 30 instances, making a total of 150 cases in which the etiology was proved. The additional 15 cases were included because purulent spinal fluid was demonstrated, and they occurred during epidemic periods of meningococcic meningitis. Excluding these 15 unproved cases, the mortality rate for the series was 4 per cent. Including all cases, the mortality rate was 5.3 per cent.

The case and mortality distribution by age was as follows:

Age	Cases	Deaths	Mortality
0-1 year	14	1	7.1%
1-5 years	27	2	7.4%
6-20 years	41	2	4.8%
21-40 years	50	0	0.0%
41-60 years	30	2	6.7%
61-80 years	3	2	
Total	165	9	5.3%

In analyzing the causes of death, it was found that six of the nine deaths occurred in the first 24 hours of hospitalization, two of these clinically being Waterhouse-Friderichsen syndromes. One death resulted from undue delay in diagnosis, and only two deaths occurred after adequate treatment.

Petechiae were found in 32.7 per cent of the cases. This is considerably less than in most military series reported, and probably indicates that the cases were seen at a later stage of the disease.

## THERAPY

In adults, 5 grams of sodium sulfadiazine in one liter of physiological saline were administered intravenously and in most instances this was followed by 1 gram orally every four hours. It was only occasionally necessary to give subsequent doses of sulfadiazine parenterally, as the Levine tube proved to be an effective instrument for the administration of medication and fluids during coma. A fluid intake of at least 3 liters a day was

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maintained, and sodium bicarbonate was given to promote alkalinity of the urine

In children, an initial sulfadiazine dosage of 0.1 gram per kilo was administered parenterally followed by oral doses calculated on a basis of 0.2 gram per kilo

In all instances an effort was made to maintain a sulfadiazine blood level of approximately 10 mg per 100 cc. The initial sulfadiazine blood levels which were determined at the end of 24 hours of treatment averaged 14.8 mg per 100 cc for 130 patients, and 95 subsequent determinations averaged 9.8 mg per 100 cc. Sulfadiazine could usually be discontinued on the ninth day of treatment.

In the 165 cases, microscopic hematuria occurred in nine instances and gross hematuria only once. No other drug reactions were encountered.

We feel that meningococcus antitoxin has a definite place in the treatment of the patient who fails to respond to sulfadiazine in 24 hours, or who on entry gives evidence of an overwhelming infection. Meningococcus antitoxin was used in 39, or 23.6 per cent of the cases. In the age group below 10 years, antitoxin was used in 32.8 per cent. In this age group, the average total dose was 20,000 units, the largest dose being 80,000 units. In the age group above 10 years, the average total dose was 50,000 units, the largest being 120,000 units. The antitoxin was given in a single dose, one half intravenously and the remainder intramuscularly. No serious reactions were encountered although eight cases developed urticaria.

In certain instances repeated lumbar punctures were done to relieve increased intracranial pressure. The indications were Biot type of respiration, undue restlessness after mild sedation and bladder catheterization, and severe headache after mild analgesics had failed to give relief. We believe that lumbar puncture, with relief of increased intracranial pressure may in the occasional case be a valuable therapeutic adjunct and even a life saving measure.

The following sequelae were encountered: (1) relapse, with subsequent recovery in a three year old child who had been discharged two weeks previously, (2) ulceration of massive purpura in a patient who had no obtainable blood pressure on entry and a blood pressure which never exceeded 70 mm Hg systolic and 40 mm diastolic for the ensuing 24 hours and who eventually recovered, (3) complete quadriplegia and respiratory paralysis which was successfully treated with a respirator and repeated lumbar punctures, (4) ptosis of the right eye and unilateral optic atrophy, (5) two instances of purulent effusions into knee joints, both of which were sterile on culture and subsequently recovered without drainage, (6) two instances of questionable hydrocephalus in infants, (7) one purulent pleural effusion which was sterile on cultures and cleared without drainage, and (8) hemiplegia in a 59 year old hypertensive who also developed thrombophlebitis of the deep calf veins.

## SUMMARY

One hundred and sixty-five cases of meningococcic meningitis with nine deaths, or a mortality rate of 5.3 per cent, have been presented. Of 150 cases proved bacteriologically, the mortality rate was 4 per cent.

Sulfadiazine was the main therapeutic weapon, but meningococcus antitoxin and repeated lumbar punctures to relieve increased intracranial pressure were valuable adjuncts in certain instances. Sequelae and causes of death have been briefly discussed.

# INFECTIOUS MONONUCLEOSIS, A STUDY OF 96 CASES<sup>1</sup>

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THE study presented in this paper was undertaken for the purpose of evaluating the clinical and laboratory findings in infectious mononucleosis, and of attempting to clarify the criteria supporting the diagnosis of this condition. This statistical analysis is based upon a series of 96 consecutive sporadic cases of infectious mononucleosis observed at the Jewish Hospital of Brooklyn over a 10 year period. This is one of the largest series of sporadic cases of this disease to be reported. Free reference will be made to the literature for purposes of comparison and evaluation of our findings.

*Definition* Infectious mononucleosis is usually defined as an acute benign infection of unknown etiology characterized by irregular fever, swelling of the lymph glands, sore throat, splenomegaly, and lymphocytosis with the presence of abnormal lymphocytes in the peripheral blood stream, the blood serum may contain antibodies against sheep erythrocytes in high titers.

*Terminology* The term infectious mononucleosis is somewhat misleading in that it suggests that the disease is characterized by the presence of monocytes in the blood. However, it enjoys the widest usage of all names which have been employed in referring to this disease. Downey and McKimlay,<sup>1</sup> in 1923, suggested "acute lymphadenosis with lymphocytosis" as a fitting name for this clinical entity. The objection was raised that this title failed to indicate the benign nature of this condition as distinguished from the fatal outcome of acute lymphoblastic leukemia, another acute lymphadenosis. To obviate this objection, it has been suggested that the disease be called "acute benign lymphadenosis." Monocytic angina, lymphocytic angina, and lymphatic reaction also have been used in referring to this condition. Glandular fever is a frequently employed term, especially when referring to an epidemic form which occurs in children.

*Historical* The first description of this disease to appear in the literature is credited to Emil Pfeiffer<sup>2</sup> who, in 1889, under the title of "Drusenfieber," called attention to a symptom-complex occurring in children, which he considered to be infectious and of epidemic nature. He was impressed by the swelling of the lymph glands along the posterior border of the sternomastoid muscles, by failure of the glands to suppurate, the splenomegaly, hepatomegaly, and the favorable course. He also noted an associated catarrhal reddening of the fauces. He pointed out that the fever declined after

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<sup>1</sup> From the Medical Service of Dr. Edmund L. Shlevin, The Jewish Hospital of Brooklyn.

several days, but glandular enlargement remained for a relatively long time

Filatow,<sup>3</sup> four years before Pfeiffer's work appeared, described cases of acute enlargement of the cervical lymph nodes without associated inflammatory changes in the mouth, nose, or pharynx

West,<sup>4</sup> in 1896, submitted the first report of glandular fever to appear in the American literature, in which he described a large epidemic in Ohio of three years' duration

Isolated reports of glandular enlargement and lymphocytosis which were mistaken for acute leukemia were made by Turk,<sup>5</sup> Hall,<sup>6</sup> and others<sup>7</sup>

In 1918 Deussing,<sup>8</sup> during an epidemic of diphtheria, separated several cases which differed from the others in that there was cervical lymphadenopathy as well as a generalized lymphadenitis with enlargement of the liver and spleen. There was a leukocytosis and marked lymphocytosis in the peripheral blood. These findings were noted in addition to the inflammatory lesions in the throat

Sprunt and Evans,<sup>9</sup> in 1920, were the first to use the term "infectious mononucleosis" instead of "glandular fever" or "Pfeiffer's disease." They stressed the benign nature of this infection, reporting a series of six cases in young adults with fever, generalized lymphadenopathy, palpable spleen, and leukocytosis with lymphocytosis. They noted that the lymphocytes in the peripheral blood were bizarre in appearance, giving quite a varied blood picture

Tidy and Morley,<sup>10</sup> in 1921, described an epidemic of glandular fever associated with lymphocytosis. They suggested that cases described earlier as acute leukemias with recovery were really examples of infectious mononucleosis. They also contended that infectious mononucleosis and glandular fever were one and the same disease

An important contribution was made in 1932 when Paul and Bunnell<sup>11</sup> discovered that blood serum of patients with the sporadic form of this disease may contain antibodies against sheep erythrocytes in concentrations far above a normal titer

## ETIOLOGY

1 *Exciting factors* The etiology of this disease has remained obscure since its earliest clinical recognition. It has come to be looked upon as a generalized infection, presenting multiple and varied manifestations which represent a protective reaction against some unknown offending agent. Whether the latter is viral, bacterial, or protozoan has never been conclusively established, although much has been written on this particular phase of the disease.<sup>12, 13, 14</sup> Staphylococci, streptococci, the spirilla and fusiform bacilli of Vincent, the *Bacterium monocytogenes hominis*, and a protozoon, *Toxoplasma*, have been suggested as the etiologic agents but none of these has been proved as such

A great deal has been written concerning the relationship of infectious mononucleosis to leukemia, syphilis, rubeola and influenza. Here again,

however, there is no conclusive proof that the association of infectious mononucleosis with these diseases indicates anything more than a coincidence<sup>15</sup>

## 2 Predisposing factors

a *Age* Children and young adults are affected for the most part. Involvement of individuals above 40 years of age is infrequent. However, any age group may be affected. Cases of infants as young as seven months of age, as well as adults up to the age of 70, have been reported<sup>16, 17, 18</sup>. In the authors' series the age varied from 1 to 61 years. The distribution of the cases according to age groups is graphically represented in figure 1.

No. of cases

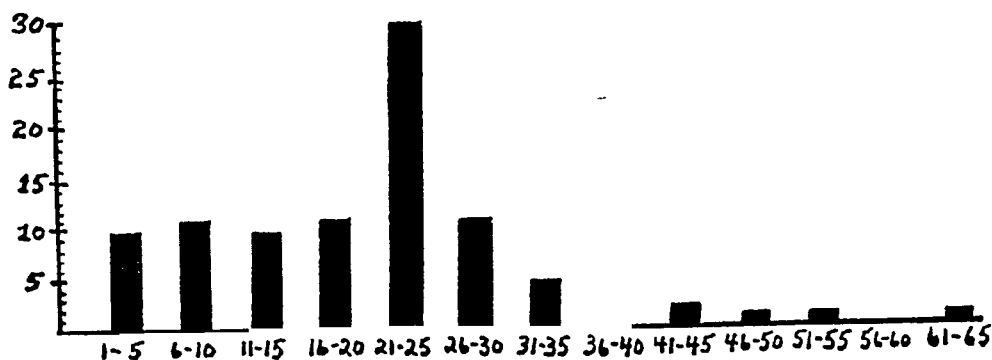


FIG 1 Age groups

Of the 96 cases studied, 83 (86.5 per cent) were between 1 and 30 years of age, 30 of these (31 per cent) were in the 21 to 25 year age group, 62 (64.5 per cent) were between 11 and 30. In Bernstein's<sup>15</sup> series of 65 cases, the age limits were 6 to 36 years, 78.5 per cent falling into the 15-30 year age group. Paul,<sup>19</sup> in his series of 51 cases, found the age limits to be 5 and 42 years, approximately 85 per cent falling into the 11 to 30 year group. Contrary to Paul's findings that only rarely was the disease observed on the pediatric service, a substantial number of the authors' cases (22 per cent) fell into the 1 to 10 year group.

b *Sex* Most authors have reported males to be somewhat more susceptible to the disease than females, usually in the ratio of 3:2<sup>20, 21</sup>. In our series this was confirmed, 54 males compared to 42 females being affected, roughly a ratio of 5:4.

c *Race* All of the cases herein reported occurred in white patients. This finding is in complete agreement with the previous literature. Only one instance of involvement of a negro has been reported<sup>22</sup>. It is felt that this is not explained by a racial predilection to the disease. Rather, it is probably due to the fact that hospitalization is not as accessible to colored people as it is to whites. In addition, their lower economic status often precludes an interruption in carrying out their occupational duties. There-

fore, it is probable that most cases of this disease occurring in the colored race are passed over as mild upper respiratory infections and the true nature of the illness is never established

*d Occupation.* The authors have found no predilection for any particular occupation. Our findings are listed in table 1

TABLE I

Students	33
Salespeople	13
Office workers	12
Infants	8
Housewives	6
Physicians, nurses, medical student	5
Lawyers	4
Unemployed	4
Chauffeurs	3
Teacher	1
Writer	1
Shipfitter	1
Governess	1
Peddler	1
Mechanical Engineer	1
Tailor	1
Soldier	1

Early reports<sup>9, 10</sup> stressed the high frequency of occurrence of this disease in individuals who were associated with hospital work, i e, physicians, nurses, medical students and laboratory workers. Our findings, as well as those of others,<sup>15, 19</sup> do not support this contention. It is felt that this impression arose because of the relatively easy accessibility of blood and serology studies to hospital workers.

*e Season.* The seasonal distribution of the case studies of the authors is illustrated in table 2

TABLE II

Season	No. of Cases	Per Cent of Total
Spring	33	34.3
Winter	25	26.0
Summer	22	23.0
Fall	16	16.7

These findings differ somewhat from those in the study reported by Bernstein<sup>15</sup> on 65 sporadic cases. Most of his cases (36 per cent) occurred in the fall season whereas only 14 per cent occurred in the spring. These statistics refer only to sporadic cases. Most epidemics of infectious mononucleosis have been reported as occurring in the spring<sup>13, 23</sup> and fall<sup>20, 24</sup>. Epidemics are rare in summer.<sup>4</sup>

*Pathology.* No autopsy material was available in our series because of the benign nature of the disease. Biopsy material, likewise, was unavailable since the diagnosis could be made by hematological and serological studies. However, Longcope,<sup>22</sup> Downey and Stasney,<sup>25</sup> Pratt,<sup>26</sup> and others,<sup>23, 27, 28</sup> have made detailed studies of the pathological changes encountered in this

disease Grossly, the lymph nodes are described as being soft and spongy and the cut surface gray and granular The outstanding features stressed by the above investigators on histological examination are hyperplasia of general and sinus reticulum, nodular foci of rounded reticulum cells, hyperplasia of follicles and germ centers in early cases and absence of follicles and germ centers in advanced cases Dense areas of small lymphocytes and looser areas in which the lymphocytes vary in size and structure are seen Large lymphocytes with pale nuclei and basophilic lymphocytes with lobulated nuclei in looser areas and sinuses are present There is more or less obliteration of structure depending upon the degree of involvement However, the architecture of the gland usually remains discernible The same abnormal lymphocytes appearing in the peripheral blood stream may be seen in the glands

*Clinical Picture* Tidy<sup>20</sup> has classified this disease into three types depending upon the predominant clinical picture, as follows (1) The glandular or Pfeiffer's type, occurring especially in children, in which the lymph node enlargement is the predominant feature (2) The anginose type (monocytic angina) This clinical picture has often been confused with diphtheria After a prodromal period of from one to three weeks, marked by increasing pyrexia and malaise, the throat becomes sore and a diphtheritic-like membrane forms on or near the tonsils and may persist for many days (3) The febrile type This is the most common type affecting adults The onset is sudden with fever, headache and malaise A macular or papular rash may then appear and not infrequently spots develop in crops The glands may not become enlarged until two or three weeks after the onset of illness The fever is of no characteristic type, is usually irregular, and persists for from one to three weeks

Although most cases can be fitted into the above classification, the latter frequently proves inadequate because of the protean manifestations of this condition Other workers<sup>20, 30</sup> have suggested a grouping dependent upon the individual sets of lymph nodes involved, emphasizing the thoracic, abdominal, and inguinal types of infectious mononucleosis

The authors agree with the conception of infectious mononucleosis as a generalized infection in which the most characteristic feature at some time in the course of the disease is an increase in the mononuclear elements of the blood<sup>15</sup> The further clinical features may then be considered and their relative importance evaluated

As stated above, the clinical features of the disease are multiple In addition, they may vary markedly in intensity Indeed, individuals may be so mildly affected that the disease completely escapes clinical recognition On the other hand, the patient may be so severely affected as to require many weeks of bed rest before recovery

There are no accurate data as to the length of the incubation period It has been reported variously as being from 1 to 28 days<sup>31, 32</sup> However, the most nearly correct figure is considered to be about 11 days<sup>10, 16</sup> Sus-

ceptibility to this disease is regarded as almost universal, but the degree of infectivity is not considered high. Epidemics have occurred especially in schools.

The type of onset varies widely. It may be sudden or gradual. The patient may present no complaints whatsoever and, indeed, the disease may go unrecognized through its entire course. More frequently, however, the onset resembles that of most acute infections with complaints of fever, headache, malaise, weakness, sore throat, chills, swollen lymph glands and gastrointestinal complaints. These may be mild or extremely severe with marked associated prostration.

Of the 96 cases of this series, the frequency of presenting symptoms is classified in table 3.

TABLE III

Fever	94	Diarrhea	4
Headache	34	Burning of eyes	3
Malaise	33	Joint pains	3
Sore throat	30	Epistaxis	2
Chills or chilly sensations	27	Sore gums	2
Weakness	22	Pruritus	2
Swollen neck glands	19	Drowsiness	2
Rash	16	Orbital pain	2
Abdominal pain	14	Chest pain	2
Nausea	13	Earache	2
Muscle aches and pains	11	Swollen inguinal glands	2
Cough	10	Dysphagia	1
Anorexia	9	Dizziness	1
Rhinitis	6	Bleeding gums	1
Vomiting	6	Convulsions	1
Constipation	5	Hematuria	1
Stiff neck	5	Painful axillary node	1
Jaundice	5	Puffy eyes	1

There were 36 subjective complaints presented in the 96 cases. The most frequent were fever (98 per cent), headache (35.4 per cent), malaise (34.3 per cent), sore throat (31.2 per cent), and chills or chilly sensations (28.1 per cent). These findings agree with those of most observers. The wide diversity of presenting complaints further testifies to the inadvisability of rigidly classifying this disease into types or groups.

A consideration of the essential physical findings in the present series of cases follows.

1 *Throat involvement* 66 cases (68.7 per cent) presented evidence of throat involvement. Only 30 of these had subjective complaints of sore throat. The findings varied from a diffuse reddening of the pharynx to a typical follicular tonsillitis. No instances of ulcerative or membranous pharyngitis were encountered. Bernstein,<sup>15</sup> on the other hand, found ulcerative lesions of the pharynx in 19 per cent of his cases and membranous pharyngitis in 7 per cent. However, the frequency of throat involvement in this study compares favorably with that of McKinlay<sup>33</sup> (78 per cent) and with that of Bernstein<sup>15</sup> (77 per cent). No complicating Vincent's stomatitis was encountered in our entire series.



2 *Glandular involvement* 76 cases (79 per cent) exhibited glandular enlargement Of these, 22 patients offered complaints of swollen lymph nodes on admission The frequency of involvement of groups of lymph nodes was as follows

Cervical	72 cases
Axillary	28 cases
Inguinal	28 cases
Epitrochlear	9 cases
Mediastinal	3 cases

Thirty-seven of the 76 cases with lymph node enlargement had involvement of two or more groups of nodes The remainder had involvement of isolated groups as follows

Cervical	37 cases
Axillary	1 case
Inguinal	1 case

In most cases the lymph node enlargement appears in the first few days of the disease <sup>4, 30, 34</sup> Less frequently adenopathy becomes evident in the second and third weeks of illness A few isolated cases have been reported in which the glandular enlargement did not appear until after 25 days <sup>35</sup>

All or any group of glands may be involved but the cervical group is pre-eminently affected The glands are almost always discrete, occasionally in clumps, have a firm rubbery consistency and are usually only moderately tender Enlargement is rarely symmetrical The glands vary in size from 1 to 4 cm

Axillary and inguinal nodes are less often involved than are the cervicals, but even the mediastinal and mesenteric groups may be involved, occasionally giving rise to pressure symptoms The frequent complaints of abdominal pain in this disease are probably on the basis of mesenteric lymphadenitis

3 *Splenomegaly* The frequency of this finding has varied greatly in different reports Davis <sup>16</sup> found the incidence to be 11 per cent in his series Bernstein <sup>15</sup> reports an incidence of 64 per cent Other workers <sup>36</sup> found splenomegaly almost in all cases ill enough to be confined to bed Tidy <sup>29</sup> considers at least 50 per cent to be the probable incidence of splenic enlargement in this condition

In the present study, the spleen was palpably enlarged in 69 cases (71.9 per cent) Of the remaining 27 cases, 20 demonstrated definite lymphadenopathy The evaluation of the presence of splenic enlargement depends upon careful and repeated palpation It is felt by the authors that 50 per cent is a very low figure for the true incidence of this finding in infectious mononucleosis

Splenic enlargement, if present at all, was made out in practically all cases at the time of admission to the hospital which, in the majority of cases, was during the first week of illness Only occasional cases developed palpable spleens under observation during the second week The degree of enlargement was only moderate in almost all cases, reaching from 1 cm to

4 cm below the costal margin. Two cases in the present series demonstrated enlargement to 12 cm below the costal arch. There have been rare instances in which the enlargement extended down to the level of the iliac crest.<sup>37</sup>

Splenomegaly may persist for weeks or even months. Baldridge et al.<sup>28</sup> reported the persistence of demonstrable splenic enlargement in a patient seven years following the acute illness.

Enlargement of the spleen without apparent lymphadenopathy was observed in 13 of the cases (13.5 per cent) studied by the authors. Absence of both splenomegaly and apparent lymph node enlargement was noted in seven cases (7.3 per cent). However, the possibility of lymphadenopathy in this group of 20 cases has not been excluded since the mesenteric, mediastinal, and other nodes not accessible to the tactile and visual senses may have been involved here. Tidy,<sup>13</sup> indeed, has stated that infectious mononucleosis without any glandular enlargement whatsoever is rare.

4 *Hepatomegaly* Here again, as in the problem of splenomegaly, reports of the frequency of this finding vary widely. Gooding<sup>23</sup> found an incidence of 3.7 per cent in his series of 27 cases. Davis,<sup>10</sup> on the other hand, reported an incidence of 100 per cent. The authors found 26 cases (27 per cent) with hepatomegaly in the present study. Of these, all but two had associated splenic enlargement. Five of the 26 cases with hepatic enlargement had no apparent associated lymphadenopathy, four of these had palpable spleens. Therefore, one of the 26 cases with hepatomegaly had neither splenomegaly nor apparent lymphadenopathy.

5 *Rash* Various types of cutaneous eruptions have been reported as occurring in this disease. Morbilliform, scarlatiniform, urticarial, vesicular, purpuric, petechial, typhoid-like, typhus-like, and other types have been described.

Paul<sup>19</sup> found cutaneous manifestations in 10 per cent of his cases. The authors found 18.7 per cent with skin lesions. These were present on admission to the hospital in practically all cases, appearing during the first few days of illness and usually lasting from one to six days. The majority of lesions observed were morbilliform in type, but urticarial, petechial, vesicular, and purpuric eruptions were also noted. Not infrequently combinations of these lesions were present.

6 *Jaundice* Jaundice was observed in five cases (5.2 per cent). Bernstein<sup>15</sup> noted this finding in 1.6 per cent of his series. All five of our cases were of the obstructive type, four being associated with hepatic enlargement. The highest icterus index observed was 164. In all cases the icterus cleared gradually, signs of improvement appearing in the second week of the disease. Four of the cases involved demonstrated associated glandular enlargement.

De Vries<sup>38</sup> has suggested the following classification of jaundice occurring in infectious mononucleosis. *Type I*, in which jaundice is the first symptom and is followed after a variable period by glandular enlargement. *Type II*, in which the jaundice appears along with glandular enlargement. Four

of our five cases belonged to this group *Type III*, in which jaundice occurs without apparent lymphadenopathy. One of our cases fell into this category.

The pathogenesis of the icterus occurring in the course of infectious mononucleosis has remained an unsettled problem. Whether it is due to glandular obstruction along the biliary tract or to an actual hepatitis is still the subject of much discussion. Morrison and Samwick<sup>39</sup> reported the presence of defective maturation of the red blood cell elements in the bone marrow of patients with infectious mononucleosis, suggesting a deficiency of erythrocyte maturation factor. This lack of the anti-anemic principle could be explained by defective absorption, storage, or utilization of same. The presence of jaundice, together with the above finding, draws attention to the liver as the site of altered physiology. Accordingly, therefore, Morrison<sup>40</sup> has suggested that the cause of jaundice in infectious mononucleosis may possibly be attributed to liver damage, either on a toxic or infectious basis. Further work, however, remains to be done before the pathogenesis of this finding becomes clear.

The significant laboratory findings in infectious mononucleosis are hematological and serological in nature.

1 *Hematological findings* Leukopenia has been reported as a frequent observation in the early stages of this illness. Paul<sup>19</sup> observed this feature in approximately 50 per cent of his series of 51 cases during the first week of the disease, the lowest count recorded being 2,000 white cells per cu mm. Bernstein<sup>15</sup> found the incidence of leukopenia in his study to be 10.8 per cent. A white blood count as low as 1,500 per cu mm has been reported in the literature.<sup>41</sup> In the present study leukopenia was observed in 38 cases (39.6 per cent), all occurring during the first week of illness. The lowest white count noted was 2,200 per cu mm. In practically all of these patients the total white cell count returned to normal or above in the second week of the disease. This sequence of events has been reported previously.<sup>19</sup> It has been suggested that the oral lesions frequently seen in infectious mononucleosis may be related to the granulocytopenia so often observed at the onset of the disease.

Of the 58 cases (60.4 per cent) without leukopenia during the first week, practically all demonstrated leukocytosis. However, the highest white blood cell counts recorded were usually noted during the second week. The vast majority of patients had white counts varying between 10,000 and 20,000 per cu mm. Only 10 patients (10.4 per cent) had counts above 20,000 per cu mm. Of these, one had a count of 32,000 per cu mm and another had one as high as 43,000 per cu mm. De Bruin<sup>42</sup> and others<sup>29</sup> report white counts as high as 63,000 per cu mm. Only about 10 instances of counts over 40,000 per cu mm have been recorded in the literature. Of these, three have occurred in adults. The one case in our series with a count exceeding 40,000 per cu mm occurred in a 23 year old female.

Lymphocytosis has been found to be the most constant feature of the blood picture which is so characteristic of this disease process. In the

present study 80 cases (83.3 per cent) demonstrated lymphocytosis. This finding was observed to be most marked during the second week of illness, but it was also present in practically all of the cases to a lesser degree during the first week. Roughly, the increase in lymphocytes paralleled the degree of leukocytosis. However, lymphocytosis was present to a significant extent even in most cases where leukopenia was observed at the onset. In the differential white blood cell counts, the lymphocytes were found to constitute from 40 per cent to 90 per cent of the white cell elements, usually from 60 per cent to 80 per cent. Reports of 97 per cent lymphocytosis and higher have appeared in the literature<sup>7, 20</sup>. Toward the end of the third week the total leukocyte count, as well as the differential white cell count, usually begins to return to normal. However, the blood picture in a case reported by Farley<sup>43</sup> maintained its characteristics for as long as six and one-half years following the original illness.

There has been much discussion concerning the character and nature of the mononuclear cells appearing in the blood stream in this disease<sup>38, 44, 45</sup>. It is felt by most authorities today that the specific cells which are responsible for the distinctive features of the peripheral blood smear in infectious mononucleosis belong to the lymphocyte series. Gall,<sup>46</sup> in his cytologic studies of this condition, came to the conclusion that these cells are atypical but relatively mature lymphocytes. They characteristically vary in size, morphology, and staining properties. The size varies from that of a small lymphocyte to that of a monocyte. The cytoplasm is typically deeply basophilic although it may be light, it may be vacuolated, giving the cell a foamy appearance. Azurophilic granules are frequently present. The nucleus may be round, oval, or indented and may occupy a portion or almost the entire cell. It may be centrally or eccentrically placed and characteristically stains deeply, the chromatin appearing in clumps. Occasionally, fenestrations may be present, an appearance produced by actual holes piercing the nucleus in various directions<sup>47</sup>. In the present series of cases studied 74 (77 per cent) showed the type of cells described above.

The red blood cell count remained essentially unaltered throughout the course of the disease in all of our cases. This is in conformity with the findings of practically all other investigators in uncomplicated cases of infectious mononucleosis and is an important point in the differential diagnosis between this disease and acute leukemia.

The blood platelet count is usually within normal limits. However, thrombocytopenia has been reported with or without an associated hemorrhagic diathesis<sup>48, 49</sup>. In the present series, only one patient exhibited a paucity of platelets with an associated bleeding tendency, this being a known case of idiopathic thrombocytopenic purpura for years preceding the episode of infectious mononucleosis.

A positive blood picture was presented by 92 of our patients (95.8 per cent). No abnormalities were noted in the remaining four cases (4.2 per cent). One of these was observed from the early stages of the disease.

through the entire course and presented splenomegaly with a strongly positive Paul-Bunnell test. The second case was seen after two weeks of illness with lymphadenopathy and a positive heterophile antibody test. The third was admitted after three weeks of the disease and presented lymphadenopathy, splenomegaly, and a positive heterophile antibody test. The fourth case was observed for the first time in the tenth week of illness and presented splenomegaly with a definitely positive Paul-Bunnell test.

*2 Serological findings* Reference has already been made to the very important contribution of Paul and Bunnell<sup>11</sup> who demonstrated the presence of an unusual type of antibody in high concentration in the blood serum of patients with infectious mononucleosis. This antibody has been called appropriately a heterophile antibody for reasons to be discussed below, and can be readily demonstrated as agglutinins against sheep red cells. It can be differentiated easily from sheep red cell agglutinins which are normally present in the blood serum in low dilutions and from other antibodies<sup>50</sup> with similar characteristics by absorption tests<sup>41, 51, 52, 53</sup>. These absorption tests can be performed without difficulty by the ordinary clinical laboratories.

Although the real significance of the presence of this antibody in high titers in the blood serum of patients afflicted with this disease remains unexplained, the diagnostic value of this finding is widely recognized. This laboratory aid has considerably facilitated the diagnosis of infectious mononucleosis.

Much has been written concerning the nature of the antibodies involved in this disease<sup>11, 50, 51, 55, 56</sup>. Forssman,<sup>57</sup> in 1911, recognized the non-specificity of certain antigen-antibody reactions. The understanding of the principles underlying these reactions is mandatory for the comprehension of the serologic phenomena encountered in infectious mononucleosis. Heterophile antigens, when injected into certain animals, call forth the production of both specific and non-specific antibodies. The latter are demonstrable by their reactions with antigens other than those involved in their production. One such is the Forssman antigen which, when injected into rabbits or serologically similar animals, causes the production of hemolysins and agglutinins against sheep red cells.

Davidsohn<sup>58</sup> applied the Forssman principle clinically in his study of the heterophile response in the blood serum of patients who had received horse serum injections. The response observed was the production of lysins and agglutinins for sheep red cells. It was shortly thereafter that Paul and Bunnell, while studying heterophile antibody responses in various diseases, discovered a high titer of such antibodies in the blood serum of patients with infectious mononucleosis. Normally sheep red cell agglutinins exist in the blood serum of most individuals, but seldom in a titer above 1:8. Following the injection of horse serum, the agglutinin titer may reach as high as 1:64 or above. The antibody normally observed in the blood serum and that appearing after treatment with horse serum are of the Forssman type. The antibody observed in infectious mononucleosis exhibits clear cut dif-

ferences from the above, readily brought out by the absorption tests referred to previously. These latter are of great value in suspected cases of infectious mononucleosis where the heterophile antibody titer is low.

In a control study of sheep red cell agglutination titers on 46 hospital cases in which a diagnosis of infectious mononucleosis was not entertained, about 9 per cent had titers of 1:64. The remainder had titers below this level, in most cases 1:8 or 1:16. In our study, therefore, titers of 1:128 or above were considered positive Paul-Bunnell tests.

In the present series reported 64 cases\* (71.1 per cent) of the 90 in which the test was performed had sheep cell agglutinin titers of 1:128 or above. Two cases had titers as high as 1:8,000. The titer was not related to the severity of the disease or to the degree of lymphocytosis. Paul<sup>19</sup> reported positive tests in 90 per cent of his series and Bernstein<sup>15</sup> found an incidence of 92 per cent. Erf,<sup>59</sup> however, noted positive reactions in only 40 per cent of his cases. Other investigators<sup>60</sup> observed positive results in half of their cases. Davidsohn,<sup>61</sup> indeed, feels that the term seronegative might have to be employed in referring to many cases of infectious mononucleosis. Further work on the agglutinin absorption tests in cases with low titers may reduce the need for the use of this term. At the present time, however, it is fair to conclude that in the presence of a characteristic clinical and hematological picture, a negative Paul-Bunnell test does not preclude the diagnosis of infectious mononucleosis.

Regarding the time of appearance of a positive heterophile antibody test in this disease, experiences differ somewhat among various investigators. Paul<sup>19</sup> found low titers in the first week of the illness with the highest titers appearing during the second and third weeks. Bernstein<sup>15</sup> observed that the test was positive when first performed almost without exception, in cases where it became positive at all, most cases being seen in the first week of the illness. He feels that the test should be repeated for a month following the onset of illness in cases with negative results. Table 4 illustrates the time of appearance of positive Paul-Bunnell tests in the study of our cases.

TABLE IV

Stage of illness	No. of cases with positive Paul Bunnell tests		
	Tested for 1st time	Became positive under observation	Total
1st week	17		17
2nd week	17	7	24
3rd week	10	3	13
4th week	4	1	5
5th week	1		1
6th week	1		1
10th week	1	1	2
12th week		1	1
			Total = 64 cases

92.1%

7.9%

It can be seen from the table that 59 of the 64 cases (92.1 per cent) with positive Paul-Bunnell tests were positive during the first four weeks of the disease. Only one case was observed to develop a positive reaction during

the fourth week, preceding studies having yielded titers within normal limits. It is worthwhile noting, however, that one case developed a positive reaction during the tenth and another during the twelfth weeks of the illness.

Table 5 demonstrates the correlation between the blood picture and the heterophile antibody tests in our series of cases.

TABLE V

	% cases with positive blood picture	% cases with negative blood picture
Positive Paul-Bunnell test	66.9	4.2
Negative Paul-Bunnell test	28.9	—

Insufficient work has been done regarding the duration of the elevated sheep cell agglutinin titer found in the blood serum of patients with infectious mononucleosis. Davidsolin<sup>41</sup> reported an average duration of 56 days in 10 cases, with extremes of 26 to 114 days after the onset of illness. In one of our cases the elevated titer disappeared two weeks after the onset of the disease, and in two cases the return to a normal level occurred three weeks after the onset. Practically all other cases were clinically improved and discharged before return of the agglutinin titer to normal limits. Bernstein<sup>15</sup> found the usual duration of elevated agglutinins to be four to five months.

The occurrence of positive Paul-Bunnell reactions in conditions other than infectious mononucleosis is quite rare aside from the increased titer of sheep cell antibodies observed in individuals treated with horse serum, a strong fact in support of the diagnostic value of the test.

Since 1928 it has been observed repeatedly that temporarily positive serologic reactions for syphilis may occur during the course of infectious mononucleosis.<sup>62, 63, 64, 65, 66, 67</sup> In a series of 70 cases studied by the authors with Kline and Wassermann tests done repeatedly in most instances, no transient falsely positive serologic reactions were encountered. Paul<sup>19</sup> noted an incidence of 8 per cent. Another investigator<sup>67</sup> found temporarily positive reactions in 18 per cent. In a study in which samples of sera were tested for from one to three months after the acute disease, Asahina<sup>68</sup> found positive Wassermann reactions in about 40 per cent. When present, the duration of the positive reaction is brief, usually lasting only a few days. This factor may be responsible for the failure to demonstrate positive serology in many cases. Kahn,<sup>69</sup> however, reports a positive reaction lasting as long as three months.

The relationship between the sheep cell antibodies and the falsely positive serologic reactions for syphilis which occur in this disease has been studied rather intensively. It has been shown quite conclusively that the antibodies concerned in the Paul-Bunnell test on the one hand and in the Wassermann reaction on the other, are unrelated.

Falsely positive Widal reactions have been observed<sup>54, 70</sup> in this disease in addition to the previously described unusual serologic changes. Three

such instances were encountered in our present series. In two of these, typhoid H agglutinins developed in titers up to 1:160, and in the third a titer of 1:320 was observed. In each case the highest titer occurred at the time of greatest positivity of the Paul-Bunnell reaction and promptly fell within two to three weeks.

*Clinical Course* The fever was irregular, varying between 100° and 106° F, usually between 100° and 103° F, with a tendency toward late afternoon and evening rises. The return of the temperature to normal was by lysis. The duration of the fever is illustrated in figure 2. The mean

No. of cases

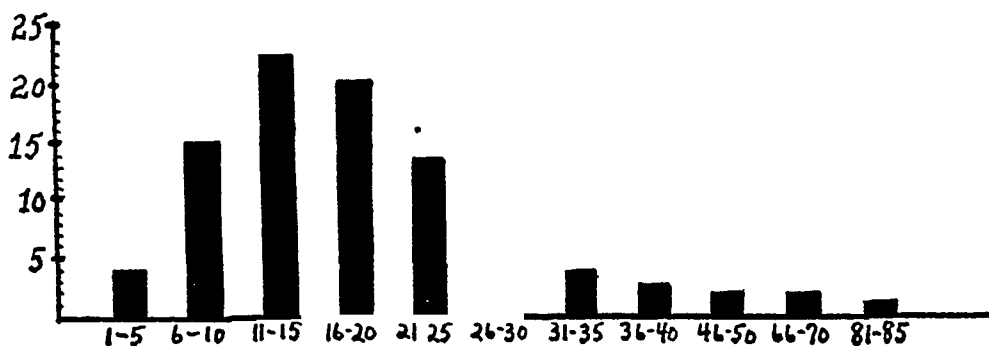


FIG 2 Duration of fever in days

duration of fever was 17 days, with extremes of three to 84 days. In 76.6 per cent of our series the febrile course lasted from six to 25 days. There was a sharp decline in the incidence of fever after the twenty-fifth day of illness. These findings agree with those of previous investigators<sup>17, 59, 71</sup>. Two of our cases were completely afebrile throughout the course of the disease. This is a very unusual feature, but Tidy and Morley<sup>10</sup> reported a similar finding in 1921.

Subjective complaints of headache, malaise, sore throat, chills or chilly sensations, weakness, abdominal pain, gastrointestinal disturbance and muscle aches and pains were frequent during the period of hospitalization, but disappeared after two to four weeks in practically all cases. Frequently, however, marked debility was observed to persist for a long period following an attack of infectious mononucleosis.

Relapses and septic complications may prolong the course of illness for many weeks<sup>16, 28</sup>. Recrudescences have also been noted not infrequently<sup>80, 80</sup>.

*Differential Diagnosis* The protean manifestations of infectious mononucleosis frequently cause it to simulate a multitude of other clinical entities. Acute leukemia is one of the foremost conditions requiring differentiation. Absence of red blood cell changes, normal platelet count and absence of immature leukocytes militate against a diagnosis of leukemia. In addition, the Paul-Bunnell test is of great aid in doubtful cases. Granulocytopenia may also be confused with infectious mononucleosis, especially during the



early stages The absence of mucous membrane ulcerations, as well as the benign course favors the diagnosis of infectious mononucleosis The heterophile antibody test here also is of help Diphtheria, Vincent's angina, Hodgkin's disease, tonsillitis, scarlet fever, typhoid fever, malaria, tuberculous adenitis, undulant fever and central nervous system infections may at times be mistaken for this disease, but hematological and serological studies should settle the issue

### SUMMARY AND CONCLUSIONS

1 A study of the findings in 96 consecutive sporadic cases of infectious mononucleosis has been presented

2 The clinical and laboratory features in this series of cases were analyzed and compared with those of other investigators in an attempt to elucidate the diagnostic criteria for this condition

3 The diagnosis of infectious mononucleosis is in order in the presence of a suspected clinical picture when the hematological findings are positive The blood smear has been the most constant and characteristic single laboratory feature in the recognition of this disease

4 A positive Paul-Bunnell test is strongly confirmatory, but its absence does not preclude the diagnosis Only occasionally is this test positive and the blood picture unrevealing in a patient presenting the characteristic clinical features of this disease It is sometimes necessary to repeat this test before a positive reaction develops

5 Because of the extreme diversity of manifestations presented, the diagnosis may go unrecognized unless the disease is borne in mind and appropriate laboratory procedures carried out

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# PHLEGMONOUS GASTRITIS AS A MANIFESTATION OF SEPSIS<sup>1</sup>

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## HISTORICAL DATA

PHLEGMONOUS gastritis has been known for many centuries Galen<sup>8</sup> described symptoms that point to an "abscess or a phlegmonous or erysipelatous tumor of the stomach" Several physicians of the Middle Ages, for instance Avicenna,<sup>1</sup> Balescon de Tarente,<sup>1</sup> Piso,<sup>1</sup> and others, dealt with this subject The first case report was written in 1594 by Forestus<sup>1</sup> His diagnosis was made clinically Since the patient recovered, we have no proof that the diagnosis was correct In 1695 Sand<sup>1</sup> published the first case where the clinical diagnosis was confirmed at autopsy Since then, reports have been more frequent In 1919, Sundberg<sup>1</sup> was able to collect 213 cases of this disease by careful and extensive studies of the past and contemporary literature In 1927, Gerster<sup>2</sup> accumulated another 47 publications including five reports of his own Konjetzny<sup>3</sup> reviewed the subject formally in 1928 In 1938 Eliason and Wright<sup>4</sup> mention 276 cases, including two of their own and 29 collected reports Since then, approximately a dozen additional presentations of case reports have appeared

## CASE REPORTS

*Case 1* S T, a colored female, 23 years old, who worked as a nursemaid, was admitted November 23, 1941 and died December 5, 1941 There was no history of abuse of alcohol or previous illness She was admitted for severe headache of two days' duration, pain in back of neck radiating to lumbar region and anteriorly to abdomen (not localized to any quadrant of the abdomen) She complained of anorexia, and weakness for the preceding few days, but no nausea or vomiting Physical examination was negative except for soft apical systolic murmur and slight injection of the pharynx

The temperature on the day of admission was 106° F, pulse 105 per minute, the blood pressure 110 mm Hg systolic and 70 mm diastolic Urinalysis showed 1 plus albumin (patient was menstruating) Blood study revealed 3,400 white cells, the differential count showed 56 per cent polymorphonuclears, 3 per cent staff forms, and 41 per cent lymphocytes, the red cell count was 3,870,000 cells, the hemoglobin 84 per cent (Sahli) All serological tests were negative, all chemical determinations were within normal limits The gastric juice was not examined Throat cultures yielded *Staphylococcus aureus hemolyticus*, *Streptococcus hemolyticus* The blood cultures on two separate occasions, i e, three days after admission and just before death, were sterile A flat plate on December 3, 1941 (two days before death) revealed marked gaseous distention (figure A) of the stomach

\* Received for publication May 16, 1944

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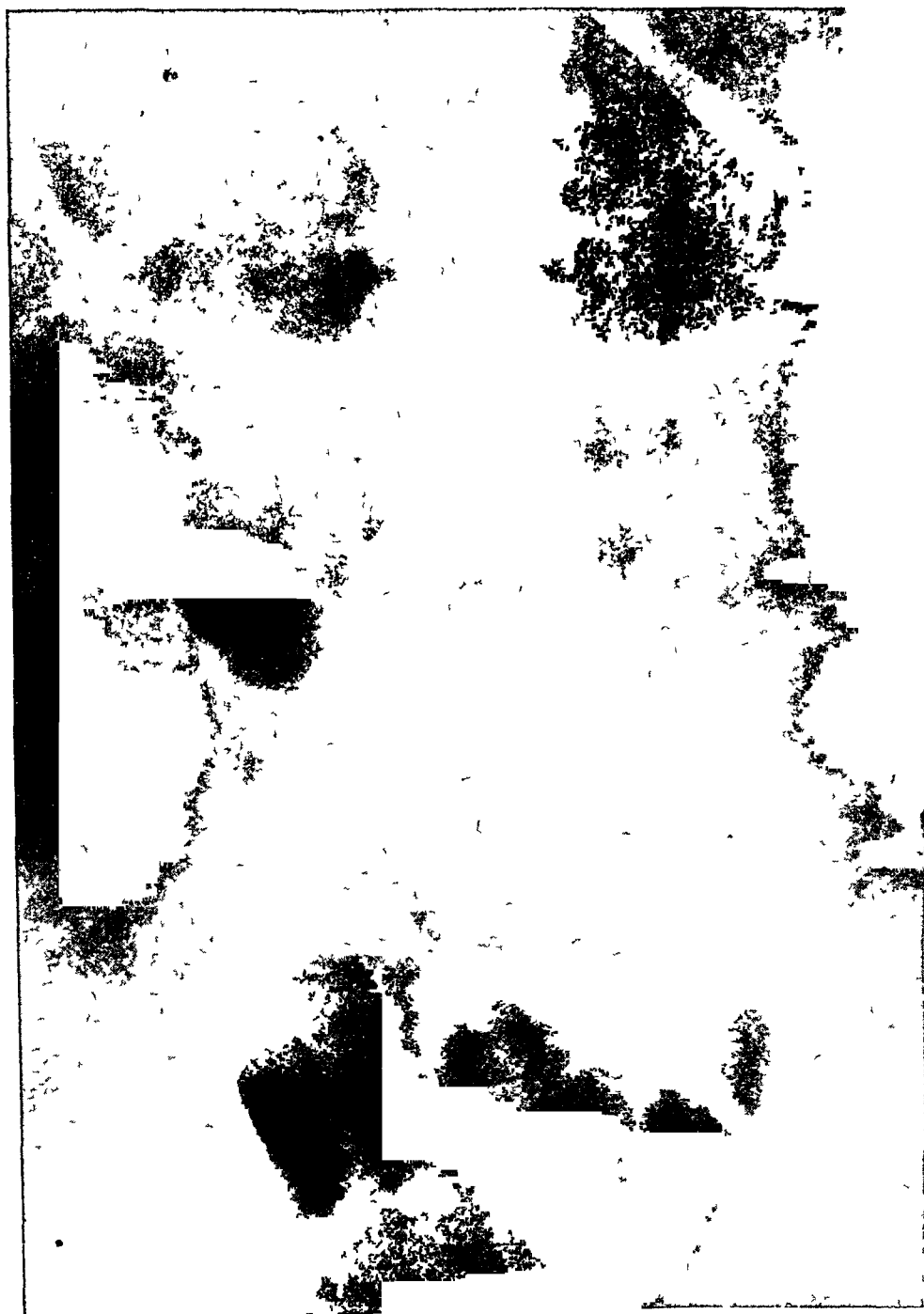


FIG A (Case 1) Roentgenogram of the abdomen showing marked gaseous distention of the stomach

*Course* On the day after admission, whitish exudate with follicles on the left tonsil were noted. There was slight injection of the posterior aspect of the drum. The temperature ranged between  $101^{\circ}$  and  $103^{\circ}$  F for the first 10 days, and then between  $103^{\circ}$  and  $105^{\circ}$  for the next five days. The patient's condition became progressively worse. She became incontinent, drowsy, and finally comatose. She died on the fourteenth hospital day, with a terminal temperature elevation of  $108^{\circ}$  F. She vomited twice on the day before death. The vomitus is described in the nurses' notes as a green fluid. (The patient received sulfapyridine during the last two days of her illness.)

At autopsy the pertinent description of the stomach was as follows. The stomach (figure 1) was dilated. On inspection some firmly adherent, yellowish sheets



FIG 1 (Case 1) Gross appearance of the stomach showing the wall thickened by edema and exudate. Mucosal folds are prominent. Note the absence of involvement of the esophagus and of the duodenum.

of exudate were present over the lesser curvature near the cardiac end. The stomach wall was greatly thickened and edematous, especially in the region of the cardia. On section it measured almost 2 centimeters in thickness at these points. The rugal folds were noted to be well preserved, although much coarser and more rounded than ordinarily noted. The mucosa was dull and granular with areas of congestion scattered in various portions, especially near the cardiac end. On inspection of the sectioned wall, there was noted a uniform, thick, yellow layer, quite soft, which extended from just beneath the mucosa down to the external muscle coat. No distinguishing characteristics could be discerned in this area, and this process, although diffusely involving the entire stomach wall from the cardiac opening to the pylorus, diminished in intensity and extent of the involvement as the pylorus was approached.

The duodenum and esophagus showed no lesion grossly.

The microscopic appearance of the stomach was as follows. The mucosa was intact without ulceration. There was a moderate amount of inflammatory infiltra-

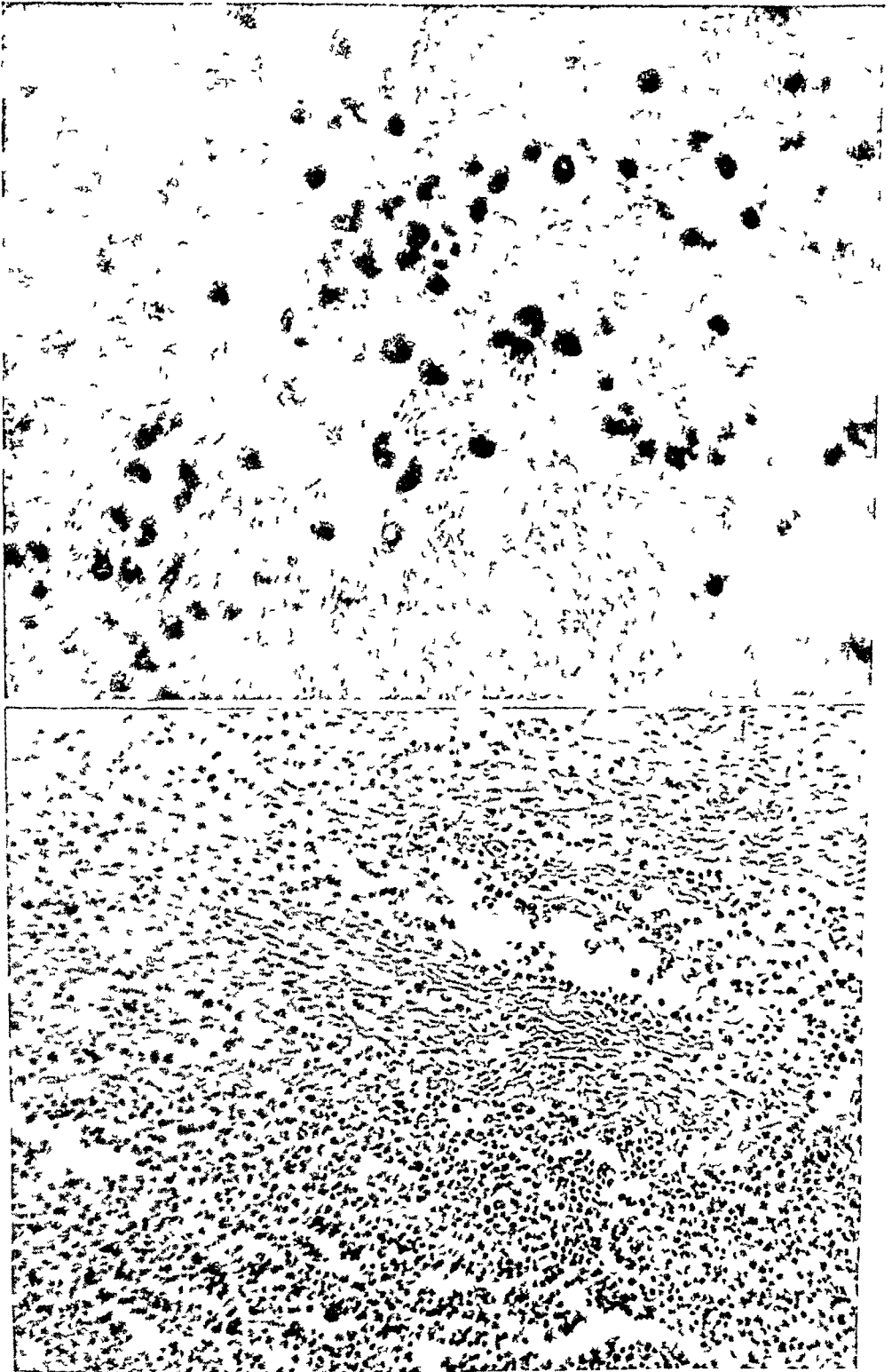


FIG 1a (above) (Case 1) H P microphotograph - Submucosa showing edema, fibrinous exudate, polymorphonuclear cell infiltration and labilized histiocytes

FIG 1b (below) (Case 1) L P microphotograph Muscular coat showing compact exudate, mainly polymorphonuclear in character Note abscess areas

tion and marked congestion. The *submucosa* (figure 1a) showed diffuse edema and fibrinous exudate. There was extensive inflammatory infiltration, lymphangitis, and venous thrombosis. In the *muscular coat* (figure 1b) the exudate was more compact. Abscess-like areas were apparently more marked than in the *submucosa*. The absence of edema may account for this appearance. There was marked lymphangitis. The *serosa* was edematous with a moderate number of inflammatory cells and some involvement of lymphatics.

The inflammatory cells of the mucosa were mainly lymphocytes. The exudate in the *submucosa* consisted mainly of polymorphonuclear cells and many labilized histiocytes. The same was true for the muscular and the serosal infiltration except that the polymorphonuclears appeared more numerous in the muscular coat.

The other pertinent anatomical findings were early peritonitis and left pleural and pericardial effusion, probably inflammatory in nature. In addition, acute hyperplastic splenitis was present.

The postmortem cultures of the peritoneum showed *B. coli*, and the left pleura showed *B. coli*, *B. pyocyaneus* and *Streptococcus non-hemolyticus*. No bacteria could be demonstrated in a histological section by Giemsa stain.

The final anatomical diagnoses were as follows: 1 Diffuse phlegmonous gastritis, with (2) extension to duodenum. 3 Early peritonitis. 4 Pleural effusion, left. 5 Pericardial effusion. 6 Acute hyperplastic splenitis. 7 Serous hepatitis.

*Discussion of Case 1* The history and physical examination in this case offer little or nothing to suggest the diagnosis of diffuse phlegmonous gastritis. The pain in the abdomen at the time of admission (12 days before death), which is described as "radiating from neck to lumbar region and abdomen," has no obvious connection with the stomach ailment. We believe that the phlegmonous gastritis appeared later. Whether the vomiting one day before death was linked to the gastric lesion is open to doubt, since the patient had received sulfapyridine at this time.

The stomach at autopsy presented the usual picture of diffuse phlegmonous gastritis (figure 1). The extension of the phlegmon to the proximal part of the duodenum is noteworthy. This is an infrequent occurrence.

We are inclined to interpret this case as a hematogenous infection. The fact that the blood was sterile up to death, however, compels the consideration of the "direct type" of diffuse phlegmonous gastritis, that is, disease produced by swallowing of organisms from the tonsillar lesion. The peritonitis is considered as an extension of the phlegmon of the stomach. The pleural and pericardial effusion may also represent extension. The marked gastric dilatation seen by flat plate is noteworthy. Though this dilatation is not pathognomonic of this lesion and there are numerous conditions that can produce this picture, yet the procedure (flat-plate) would seem to be distinctly indicated.

*Case 2* First admission January 12, 1942. Discharged April 21, 1942. Final admission May 15, 1942. Died May 29, 1942. E. M., an 11 year old colored girl, was admitted for painful cervical lymph node swelling, anorexia, fatigue, weight loss and migrating joint pains. There was a history of cough with blood-streaked sputum one year before admission.

Physical examination revealed a poorly nourished and poorly developed colored female with many enlarged, hard, discrete cervical, axillary, inguinal and epitrochlear



nodes The parotid salivary glands also were swollen The corrected sedimentation rate was 22 millimeters per hour The patient was afebrile Blood studies revealed 6,950 white cells, 32 per cent polymorphonuclears, 68 per cent lymphocytes, 3,800,000 red cells and a hemoglobin of 78 per cent (Sahli) Roentgenogram of the chest revealed large hilar nodes

*Course* After two weeks, the patient began to run a low grade fever At six weeks she developed a butterfly rash over the face A biopsy of the skin lesion and deltoid muscle suggested lupus erythematosus disseminatus Eight weeks after admission, she developed a submental abscess which drained spontaneously After that the temperature fell to normal and she improved generally An electrocardiogram on April 6, 1942 showed changes similar to those of an anterior coronary occlusion Two weeks later an electrocardiogram showed sinus tachycardia with left axis deviation and ST and T wave changes similar to those in active rheumatic carditis The patient was discharged during the fourth month of hospitalization She returned three weeks later because of weakness, left chest and precordial pain, dyspnea on exertion, and cough Difficulty in urination and frequency were also present Physical examination, in addition to earlier findings, revealed an injected pharynx, enlarged heart with sounds of poor quality and a short apical systolic murmur The white cell count at this time revealed 6,000 cells, 80 per cent of them being polymorphonuclears, 20 per cent lymphocytes The red cell count was 4,000,000, the hemoglobin 75 per cent (Sahli) The corrected sedimentation rate was 42 millimeters per hour The urine showed 1 plus albumin The temperature was 102° F The roentgenogram of the chest on May 16, 1942 showed moderate thickening of lung roots with a few calcified hilar nodes, peritruncal thickening in the right lower lobe and right interlobar pleural thickening

*Course* Four days after readmission (May 19, 1942) she developed right pleural fluid A chest tap yielded purulent material A closed thoracotomy was done On May 24, 1942, while chest fluid was being withdrawn a second time, the child had a clonic-tonic convulsive seizure for one to two minutes The temperature remained high (from 101 to 104° F) The white cell count rose to 26,000 The urine on May 26, 1942 showed granular and hyaline casts On May 28, 1942, the day before death, the child developed coarse râles bilaterally, and the pulse became rapid and thready She was confused at times Twelve hours before death the patient complained of abdominal pain and vomited a large amount of dark green watery fluid Four hours before death, she vomited again The vomitus is described by the nurse as "a dark brown curdled substance with many threads of mucus" The nurse's note two hours before death reads again "patient vomited about three ounces of dark brown mucus" (Patient received sulfadiazine at that time) The temperature rose to 104° F terminally The child died the fourteenth hospital day of the second admission and five months after the onset of symptoms A blood culture (May 23, 1943) and cultures of pleural fluid (May 18, 1942 and May 24, 1942) revealed pneumococcus type 21 A blood culture (May 28, 1942) showed pneumococcus type 21 and *Streptococcus non-hemolyticus* An electrocardiogram (May 28, 1942) showed sinus tachycardia

At autopsy the pertinent description of the stomach was as follows The wall of the stomach was markedly thickened throughout, measuring 7 to 8 millimeters in diameter This thickening began abruptly at the cardia and ended abruptly at the pylorus On section, the wall revealed infiltration by semiopaque grayish white material apparently in all coats of the stomach with the markings lost There were numerous irregular, superficial ulcerations of the mucosa throughout, varying in size from 2 to 8 millimeters in diameter

Microscopically the stomach showed the following picture The mucosa appeared somewhat edematous There was a moderate amount of cell infiltration, and digestive

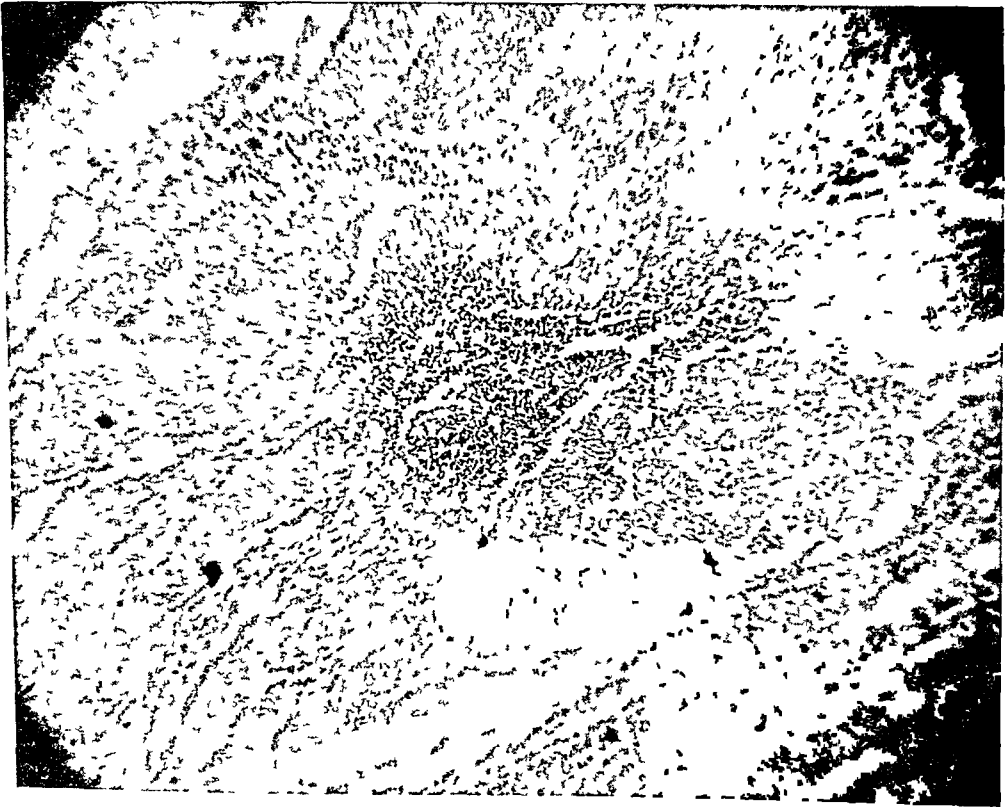
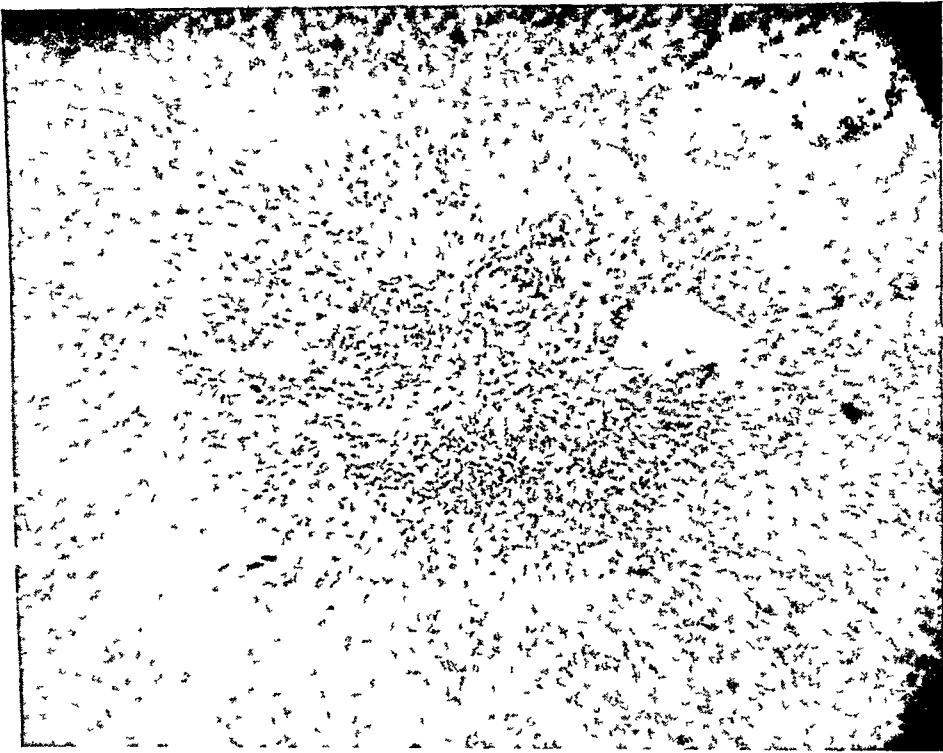


FIG 2a (above) (Case 2) L P microphotograph Submucosa with extensive exudate. Small part of muscularis mucosae and mucosa shown above. Note vascular thrombi.

FIG 2b (below) (Case 2) L P microphotograph Muscular coat showing cellular exudate with abscess formation.

erosions and ulcerations of the mucosa. The ulcers extended through the muscularis mucosa into the submucosa with marked basophilic staining of autolytic zones. This basophilia was particularly true for the basement membrane, reticulum, collagen material, and muscle. The *muscularis mucosae* showed some edema in areas which were not involved by ulceration. There was a limited amount of inflammatory cell infiltration. The *submucosa* (figure 2a) presented marked swelling and edema with extensive cell infiltration. Thromboses of venous channels and lymphatics were outstanding. The walls of some veins and lymph channels showed inflammatory infiltration. Intervening diffuse cellular exudate with some breakdown into abscess formation was present. The *muscular coat* was extensively involved by inflammatory exudate, particularly in areas of penetrating venules with thromboses of same. There were regional abscess areas with some destruction of muscle (figure 2b). The *serosa* showed edema with a considerable amount of inflammatory cells. Vascular channels were not included in the serosal sections. The inflammatory exudate consisted mainly of polymorphonuclears throughout.

The autopsy revealed the pathologic lesions of lupus erythematosus disseminatus as well as the findings produced by sepsis. The pertinent findings demonstrating sepsis were superimposed bacterial growth on the atypical verrucous endocarditis, infected pleural effusion, organizing bronchopneumonia, hyperplastic splenitis, and finally phlegmonous gastritis and peritonitis.

The postmortem culture of the pleural fluid revealed pneumococcus type 21, *Staphylococcus aureus*, and *Streptococcus non-hemolyticus*. A postmortem culture of the peritoneum yielded pneumococcus type 21, *B. coli*, *Streptococcus hemolyticus* and *Streptococcus non-hemolyticus*. A culture from the mitral valve vegetation showed overgrowth by *B. coli*. Giemsa stains of a tissue section revealed large numbers of cocci with the morphology of diplococci in the submucosa, muscularis and serosa. Only very few cocci could be demonstrated in the muscularis mucosae and none in the mucosa.

The final anatomical diagnoses were as follows: 1 Lupus erythematosus 2 Generalized lymphadenopathy 3 "Wireloop" lesion of kidney 4 Chronic active pericarditis 5 Organizing bronchopneumonia 6 Bilateral pleural effusion—infected 7 Atypical verrucous endocarditis (Libman-Sachs) of mitral and tricuspid valves 8 Superimposed bacterial endocarditis 9 Septicemia—pneumococcus type 21) 10 Phlegmonous gastritis 11 Peritonitis

*Discussion of Case 2* In this case the history and physical examination are slightly more suggestive of diffuse phlegmonous gastritis than in the first case. Twelve hours before death the child complained of abdominal pain (no exact description given) and vomited three times. In view of the pain we are inclined to attribute the vomiting to the stomach lesion, even though this patient had received sulfadiazine at this time.

The gross and microscopic findings in this case do not differ from the vast majority of reports of diffuse phlegmon of the stomach.

This case is interpreted as a case of lupus erythematosus disseminatus with bronchopneumonia and infected pleural effusion which led to blood stream invasion with manifestation of the latter in the superimposed bacterial infection of the existing endocarditis, as well as the phlegmonous gastritis. The peritonitis again should be considered as an extension of the stomach lesion. The positive blood culture is in favor of this concept.

*Case 3* Admitted January 9, 1942. Died January 9, 1942. C. P., a 70 year old white male, was brought to the hospital in extremis. A fragmentary history

obtained from a son revealed that he had been ill with "chronic cough and heart trouble" for many years. Shortly before admission he became comatose and incontinent. There was no history of acute upper respiratory infection. Physical examination revealed an elderly white male in extremis. The ear, nose and throat examination revealed no lesion. The heart was not enlarged. No thrills or murmurs were heard. Apparent abdominal tenderness existed, for the patient grimaced when the abdomen was palpated. The patient died before a physical examination or laboratory studies could be completed.

At autopsy the pertinent description of the stomach was as follows. On opening the peritoneal cavity, a massive stomach was seen occupying almost the entire upper half of the abdominal cavity. The wall of the stomach (figure 3) was markedly indurated. The serosal surface near the fundus was covered by a small patch of



FIG 3 (Case 3) Gross appearance of the stomach showing marked dilatation and visible thickening of the stomach wall. Note the absence of involvement of the esophagus and the duodenum, and the numerous polypoid mucosal protrusions. Portion of aorta with enlarged adventitial lymph nodes is seen above.

friable, yellowish white exudate. The serosa was otherwise thin and glistening throughout. On section the entire stomach wall was seen to be markedly thickened, measuring at least  $1\frac{1}{2}$  cm in thickness at its widest portion. The area of thickening extended throughout the entire stomach, from the cardiac orifice to the pylorus. The lesion was well demarcated from the regional esophagus and duodenum, which showed no gross evidence of the changes noted in the gastric wall. The muscularis was markedly thickened, with a definite translucency suggesting edema noted throughout. The submucosa was markedly thickened and edematous with many well demarcated, frankly necrotic areas scattered irregularly throughout. The mucosa appeared intact although it was moderately thickened. No evidence of ulceration was noted. There were seen approximately 10 large polypoid mucosal protrusions ranging in size from

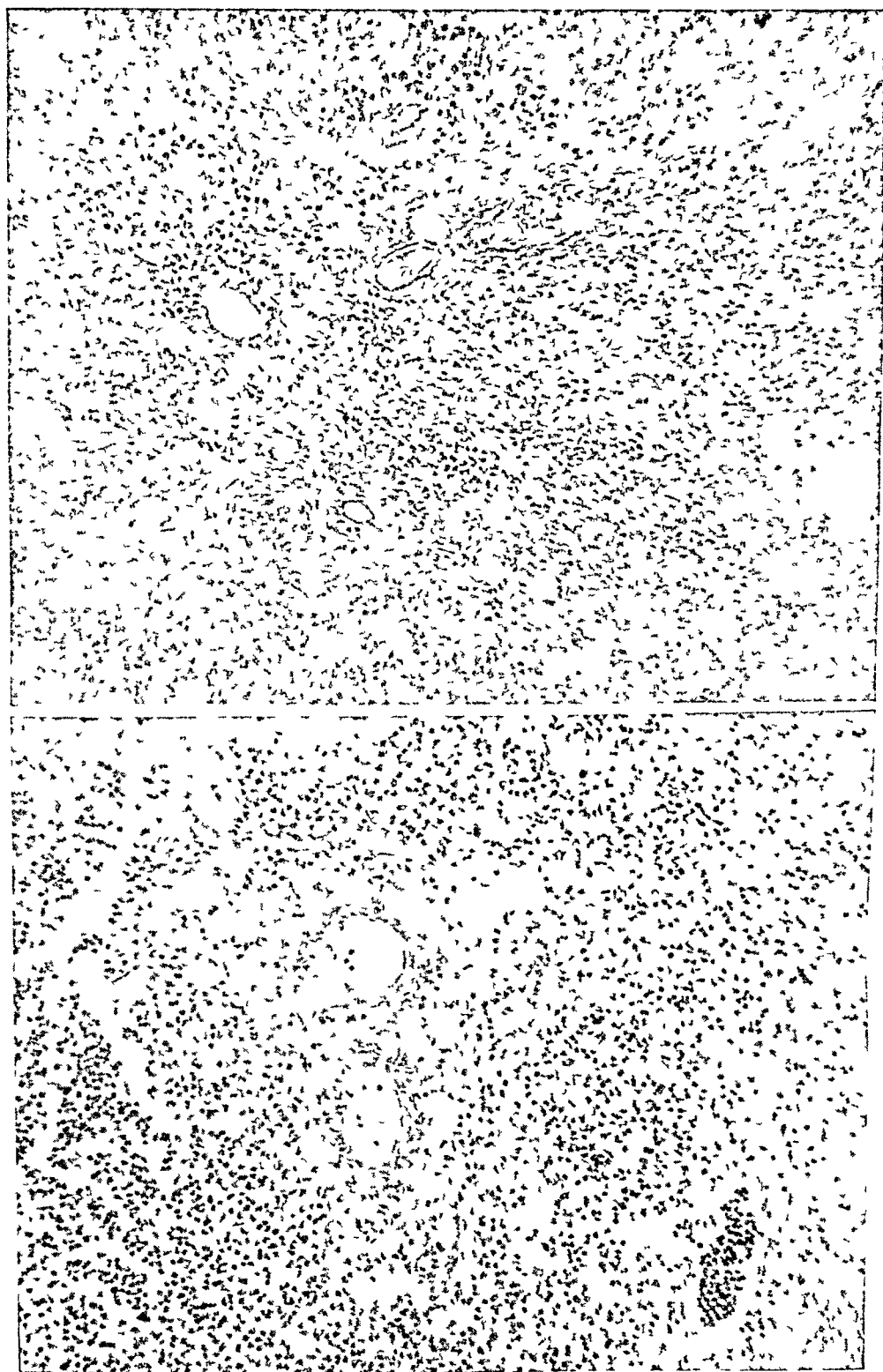


FIG 3a (above) (Case 3) L P microphotograph Submucosa presenting arteritis, thrombi formation and diffuse exudation

FIG 3b (below) (Case 3) L P microphotograph Submucosa showing extensive polymorphonuclear exudate, fibrin about vessels, and a dilated lymphatic channel filled with cells, a prominent feature in this case

½ to 2 cm These polypoid structures were produced by protrusion of the underlying edematous swollen submucosa

The microscopic appearance of the stomach was as follows The *mucosa* showed extensive infiltration by inflammatory cells with separation of the glands which showed also dilatation and intestinal metaplasia No ulceration was present The *muscularis mucosae* presented cell infiltration which was more prominent in the deeper layer In the *submucosa* (figures 3a and 3b) there was seen abundant fibrin, diffuse and extensive cellular infiltration with small abscesses and necrobiotic areas The dilated lymph vessels were tensely filled with cells Arteries and veins showed extensive inflammatory infiltration of the adventitia and media with prominent accumulation of fibrin surrounding veins, arteries and lymph channels, and fusing them together Small hyaline thrombi were noted in capillaries, and cellular and fibrinous thrombi in small veins The *muscularis* showed separation of bundles by edema and frank purulent exudate and fibrin with abscess formation Some venous thrombi were present and distended lymphatics were filled with cells and fibrin In the *serosal layer* the swelling was not marked, but there was considerable inflammatory infiltration and lymphatic distention

The inflammatory cells of the *mucosa* were mainly lymphocytes, some large mononuclear cells, and very few polymorphonuclears The *muscularis mucosae* showed similar exudate, more prominent in the deeper layers of the structure with the polymorphonuclears more numerous The *submucosa* presented mainly polymorphonuclear exudate and the same was true for the *muscularis* which showed a few large mononuclear cells in addition

Other noteworthy findings were early peritonitis, hyperplastic splenitis, hyperplastic lymphadenitis, and bilateral lower lobe bronchopneumonia

Postmortem culture of the stomach revealed *B coli*, *B proteus* and *Streptococcus hemolyticus* Culture of spleen and peritoneum yielded *Streptococcus hemolyticus* Large numbers of cocci arranged in short chains were seen with the aid of Giemsa staining in the *submucosa* and in the *muscularis* In the *serosa* the same organisms were found in diminishing numbers No organisms could be located in the *muscularis mucosae* or *mucosa*

The final anatomical diagnoses are as follows 1 Diffuse phlegmonous gastritis, with polypoid protrusions 2 Chronic gastritis 3 Limited peritonitis 4 Hyperplastic splenitis 5 Hyperplastic lymphadenitis 6 Sepsis (*Streptococcus hemolyticus*) 7 Bilateral lower lobe bronchopneumonia

*Discussion of Case 3* The history and physical examination were fragmentary and incomplete The known data were irrelevant except for the grimacing on palpation of the abdomen This finding in a comatose and moribund patient suggests severe tenderness

The outstanding autopsy findings were the size of the stomach and the presence of about 10 polypoid protrusions into the lumen The great enlargement of the stomach (it occupied almost the entire upper half of the abdomen) was due mainly to extreme dilatation This feature of dilatation may be demonstrated by roentgen-ray as in case 1 (figure A), and this clinical form of the disease may be diagnosed by this means The presence of multiple polypoid structures of the *mucosa* is a rather rare phenomenon Except for the above mentioned facts this case differs little anatomically from the majority of published cases

In view of the inadequate history and physical examination this case cannot be analyzed fully in regard to its etiology or pathogenesis We are

tempted, nevertheless, to consider this a case of bronchopneumonia in a 70 year old man with sepsis following, and the stomach lesion occurring as a manifestation of the latter. The peritonitis, as in the first two cases, should be considered as an extension of the inflammatory process from the stomach. The presence of a chronic gastritis in this instance makes it difficult to rule out completely the local origin of the phlegmonous lesion of the stomach (direct route). The chronic gastritis obvious in the microscopic examination represents a preexisting lesion possibly on the basis of stasis of known cardiac decompensation of many years' duration.

In addition to the three cases described above, which exhibit the classical picture of diffuse phlegmonous gastritis at the autopsy table and under the microscope, we wish to report another case which seems appropriate.

*Case 4* Admitted November 29, 1943. Died December 3, 1943. L. S., a two year old white male infant, was admitted with complaints of nausea, vomiting and fever since the morning of admission. Physical examination revealed a comatose child with multiple petechiae. The pharynx and tonsils were slightly injected. The heart sounds were distant. The pulse was barely palpable. The blood pressure was 44 mm Hg systolic and 32 mm diastolic. The laboratory data were as follows: 17,800 white cells, 49 million red cells, 90 per cent hemoglobin (Sahli), 76 per cent polymorphonuclears, 24 per cent lymphocytes. The spinal fluid showed 8 lymphocytes, no other cells. The urine was positive for albumin.

*Course* The child ran a high temperature (to 103.8° F), the pulse ranged between 130 and 158 per minute. He vomited several times. On the third hospital day he developed nuchal rigidity and a positive Kernig sign. The child died on the fifth hospital day. Blood and spinal fluid cultures before death were positive for meningococcus type 1.

On postmortem examination the stomach (figure 4) appeared moderately enlarged. The serosa was glistening with a slight loss of translucency. On opening along the greater curvature, the stomach wall was found to be diffusely thickened, measuring between 1.2 and 1.4 cm in width. The mucosa was thrown up into thick folds, in areas covered with mucoid material, and showed multiple minute areas of blood extravasation. On cut section the mucosa itself did not appear to be thicker than usual. In contrast, the submucosa appeared many times the normal thickness. It was sponge-like and porous in appearance in areas, glistening and translucent elsewhere. The muscle also appeared translucent. The swelling of the stomach wall stopped abruptly at the duodenum and somewhat more gradually in the esophageal region.

Microscopic examination of the gastric wall showed edema of the mucosa proper and extensive edema of the submucosa throughout (figure 4a), with wide separation of the supportive tissue and collagen by non-staining and staining fluid. Only a few large mononuclear cells were present in the exudate. In the submucosa, a vessel filling all of the 4 mm high-power aperture showed a central antemortem thrombus occupying about half the lumen of the vessel.

Giemsa stains failed to reveal any organisms throughout the stomach wall or in the serous exudate. Cocci resembling meningococci were seen within the thrombus described above.

Though not altered grossly, under the microscope the esophagus presented some subepithelial edema towards the gastric end.

The pertinent autopsy findings were an early meningitis and adrenal hemorrhage.

The final anatomical diagnoses were 1. Septicemia (meningococcus) with

petechiae 2 Adrenal congestion and hemorrhage (Waterhouse-Friderichsen syndrome) 3 Subserosal edema of stomach 4 Early meningitis

*Discussion of Case 4* It is our impression that this case represents a first stage of a diffuse phlegmon of the stomach before suppuration and necrosis had set in. This early lesion has been observed in only a few instances, and warrants presentation because of theoretical implications.

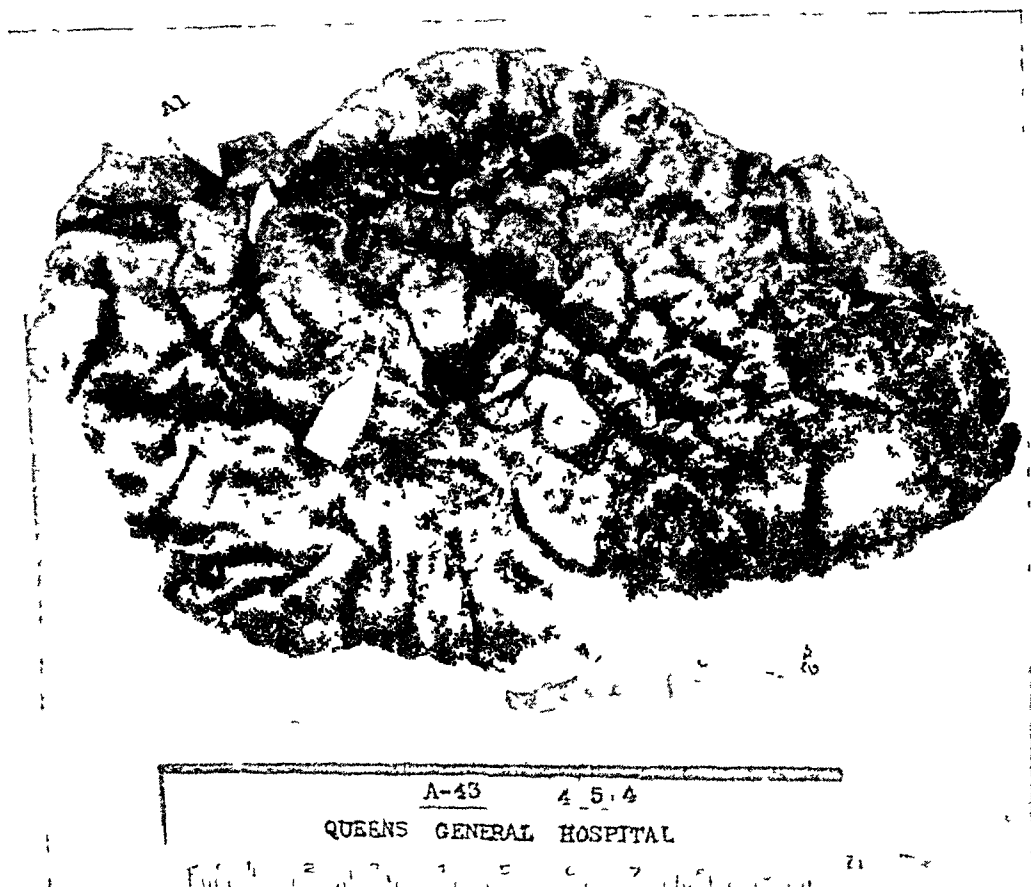


FIG 4 (Case 4) Gross appearance of the stomach. Note edematous, prominent mucosal folds. Central arrow points to minute mucosal hemorrhage. Arrow A1 points to the duodenum where the edema ends abruptly. Arrow A2 points to the esophagus, which shows some edema present.

Contini<sup>19</sup> produced marked edema of the submucosa in one of his rabbits by intravenous injection of streptococci. Herrmann<sup>1, 3</sup> and Berka<sup>3</sup> mentioned the fact that in some cases of phlegmonous gastritis the greatly thickened stomach wall can be compressed to normal thickness. This was true in this instance, we could reduce the thickness of the wall by pressure from 1.4 cm to 0.4 cm. The vomiting, nausea and fever might be considered symptoms of the gastric lesion. The time factor does not favor this interpretation, and these symptoms are all better explained on the basis of the meningococcus sepsis and meningitis.



The *similarity* in the type of exudate seen in the meninges and the stomach is distinctly noteworthy. The positive blood culture and the petechiae on admission, as compared with the appearance of the meningeal signs only on the third day of illness, favor consideration of the meningitis and early gastritis as parallel lesions of later localization. Both sites show only very minimal and similar cell exudate. In passing, we might mention



FIG 4a (Case 4) L P microphotograph showing extensive edema of the submucosa with wide separation of the supportive tissue and collagen by non-staining and some staining fluid. A few large mononuclear cells are present in the exudate. Note thrombus in small venous channel. A small part of the muscularis mucosae and mucosa is included in the photograph.

that to our knowledge no other cases are known in which this condition was produced by the meningococcus.

#### GENERAL DISCUSSION

In 4,007 autopsies performed at Queens General Hospital from October 1935 to the end of 1943, three cases showed a fully developed picture of phlegmonous gastritis, and a fourth one showed what suggests the earliest

stage of the disease. In none of the patients did a history or physical examination suggest the condition. The diagnosis was not made clinically in any of the cases.

There was no instance of preexistent mucosal defect such as carcinoma, ulcer, operative wound, etc., which could be considered a portal of entry for invading organisms, suggesting the "direct route" of infection. We believe that in cases 2 and 3 the infection definitely occurred via the blood stream, even though a chronic gastritis was present in the latter. In case 1 the possibility of direct infection by swallowing of organisms cannot be excluded entirely, but the absence of a portal of entry in the stomach mucosa favors the hematogenous route. If case 4 represents the first stage of phlegmonous gastritis, as we assume it does, then it belongs to the hematogenous group.

In contrast to Konjetzny,<sup>3</sup> Gerster,<sup>2</sup> Eliason and Wright<sup>4</sup> and many others it is our opinion that the hematogenous route of infection is the usual one. We wish to compare the process with that occurring in phlegmonous cholecystitis observed in septic conditions. The macroscopic as well as the microscopic picture of gall-bladders in phlegmonous cholecystitis is very similar to that seen in phlegmon of the stomach. The frequent occurrence of cholecystitis, with or without stomach involvement, in Rosenow's<sup>18</sup> experiments is in favor of our concept for the pathogenesis for both entities. Wilkie's<sup>22</sup> experimental production of cholecystitis by streptococcus injections point in the same direction. (See below for discussion of pathogenesis.)

We wish to report for comparison a case of phlegmon of the gall-bladder that illustrates the hematogenous route of infection and resembles closely the above described cases of phlegmonous gastritis.

O. T. Admitted April 28, 1941. Died May 8, 1941. This 25 year old white primipara was admitted to Queens General Hospital because of a sudden rise of blood pressure (144 mm Hg systolic and 94 mm diastolic). On admission she was in labor, with ruptured membranes, and a stillbirth was delivered by breech extraction. Her postpartum course was marked by temperature rise, elevation of urea nitrogen from 12 to 160 mg per cent, creatinine elevation to 6.8 mg per cent, albuminuria, pyuria, hematuria, and finally anuria. Her white cell count rose to 21,200 with 84 per cent polymorphonuclear leukocytes. The temperature was spiking to 105° F. She lapsed into coma and died the sixth postpartum day.

An antemortem urine culture and blood culture revealed *B. coli*.

At autopsy the gall-bladder was found to be dilated. The lumen contained dark greenish bile. The mucosa was slightly granular, with some focal areas presenting a lighter yellow color. No calculi were found, and no unusual features were seen in the extrahepatic bile ducts.

Microscopically there was marked edema of all layers with extensive inflammatory infiltration. The mucosa showed desquamation of most of the epithelial tissue suggesting postmortem autolysis. One area of ulceration was present with bile staining. The ulcer bed extended through the muscular coat and showed destruction of muscle and collagen with extension to the walls of some blood vessels. One vessel just beneath the ulcer bed showed a hyaline thrombus. The subepithelial

*stroma* showed extensive inflammatory infiltration and edema. The underlying muscle bundles were widely separated by edema, by compact cellular exudate, or zones of scant inflammatory cell infiltration. Beyond the muscle layer there was distinct edema of the collagen with swelling. There was considerable non-staining edema of the *subserosal* fatty tissue. In this coat some perivascular infiltration was present, but the exudate was quite limited in the outermost zones of the external coat.

In the mucosa the inflammatory cells were large mononuclears, some lymphocytes, and a few polymorphonuclear cells. Some large fibroblasts were seen in the exudate. In between the muscle bundles the exudate had a distinct monocytic appearance with some lymphocytes. The serous coat showed only focal accumulation of inflammatory cells with large histiocytes and ordinary monocytes predominant throughout. Giemsa stains revealed small bacilli in the bed of the ulcer described above and in the regional wall.

The final autopsy findings were: 1 Acute bilateral suppurative pyelonephritis with uremia (clinical) 2 Acute cystitis 3 Sepsis (*B. coli*) 4 Phlegmonous cholecystitis 5 Purulent bronchitis 6 Hyperplastic splenitis 7 Toxic hepatosis 8 Status postpartum with laceration of vagina and hemorrhage.

## DISCUSSION

Infection of the gall-bladder can occur via two avenues, as in the case of infection of the stomach wall. Infection of the contents of the lumen of the gall-bladder can occur obviously by an organism which will not be devitalized by bile. The typhoid salmonella group does match such requirements, and some of our acute and chronic cholecystitis lesions in typhoid may represent infection of the wall from the lumen. The lumen becomes infected by secretion of organisms through the liver as a result of portal circulatory invasion by bacteria. Experimental work demonstrating this has been done with *S. typhi muenum*. Yet in some cases of typhoid, cholecystitis has been evidenced by the fact that the wall of the gall-bladder itself contains the organisms when the contents of the gall-bladder fail to do so.

This last situation corresponds to what might be expected on theoretical grounds with the gram positive cocci on the basis of bile action on such organisms, and by the experimental evidence offered by Wilkie<sup>22</sup> and Rosenow<sup>18</sup> and others. Cultural studies of the gall-bladder confirm this finding, for the organism is more readily cultured from the sentinel node or gall-bladder wall than from the bile contents.

It would be natural to expect then that in cases of sepsis where a bacteremic seeding of tissue is possible, the gall-bladder wall might simulate the submucosa of the stomach and become a site for secondary localization of the infection. Of interest in this connection is the controversy still existing in histology as to whether the gall-bladder does represent the equivalent of the coats of the gastrointestinal tract through the submucosa only.

It is our impression that phlegmonous cholecystitis and phlegmonous gastritis have identical mechanisms with a pathogenesis which predicates a general bacteremia with secondary localization in the loose tissue and stroma of the wall of such organs. It is our impression that this is not so rare an

occurrence for both the stomach and the gall-bladder as the current literature would seem to indicate

*Pathogenesis* Many complex classifications of phlegmonous gastritis have been offered Sundberg<sup>1</sup> separates phlegmonous gastritis into two forms (a) the form which follows direct implantation of infectious material into the stomach wall, and (b) the form that follows as a result of a metastatic hematogenous process

There still is a lot of controversy in regard to the pathogenesis of phlegmonous gastritis In some papers, particularly in the earlier ones, the disease is considered to be metastatic (Brand,<sup>1</sup> Krause,<sup>1</sup> Manoury,<sup>1</sup> Rokitsanski,<sup>1</sup> Brinton,<sup>1</sup> Klebs,<sup>1</sup> v Meyenberg,<sup>3</sup> Dittrich,<sup>11</sup> Lowenstein,<sup>3</sup> Obendorfer,<sup>3</sup> Simmonds,<sup>3</sup> Baird,<sup>3</sup> and Nawerck<sup>3</sup>) The majority of authors stress the direct manner of infection in their cases Sundberg,<sup>1</sup> in reviewing 215 cases, comes to the conclusion that the metastatic hematogenous type is extremely rare Konjetzny<sup>3</sup> agrees with him by stating that "proof of this mode of infection is extremely scarce as yet" Gerster<sup>2</sup> and E Krause<sup>11</sup> are of this same opinion Rokitsanski's<sup>1</sup> conclusion is that, at least in puerperal sepsis, the occurrence by hematogenous route is very rare Eliason and Wright<sup>4</sup> consider the majority of the cases to occur via "intra-gastric infection" Bockus<sup>17</sup> states that the disease is either produced by bacteremia or mucosal damage, and so accepts both modes of infection without giving any preferences to one or the other route

Experimental evidence indicates that both forms of infection exist Rosenow<sup>18</sup> injected streptococcus cultures into animals in an effort to produce gastric ulcers In one experiment a rabbit showed at autopsy "what appeared as a phlegmonous gastritis" in addition to cholecystitis, nephritis, endocarditis, etc Rosenow does not mention the microscopic appearance in this case In another animal he describes the histological picture of the stomach lesion as follows "Section through the base of the ulcer showed in the center complete absence of mucous membrane and submucosa, and necrosis of one-third of the circular layer of the muscular coat There was leukocytic infiltration between the disintegrating epithelial cells, in the submucosa, chiefly around vessels, along the connective tissue stroma, between muscle-bundles and beneath and in the thickened and adherent peritoneal coat" He notes "thrombosed vessels running at right angles to the floor of the ulcer and two large thrombosed vessels in the submucosa" and "marked leukocytic infiltration surrounding the thrombosed vessels in submucosa Gram-Weigert stains showed a moderate number of diplococci chiefly in the area of leukocytic infiltration and a few in one of the thrombi"

This is the most comprehensive microscopic description we could find in Rosenow's paper If this is a fairly representative picture of the ulcerative stomach lesions he encountered so often in his experiments, we wonder if he did not deal with a phlegmonous gastritis in many more of his cases At least the above microscopic picture is almost identical with what we and other authors describe as the classical finding in the stomach phlegmon This

would imply Rosenow did not produce "the usual ulcer" assuming that he means by this the chronic peptic ulcer of man. The fact that the experimental animal often showed endocarditis, myocarditis, nephritis, cholecystitis, etc., in other words lesions that must be considered manifestations of the hematogenous infection, confirms our concept of the mechanisms involved. Rosenow's work at least in one experiment, and probably in others, demonstrates the metastatic route.

Ashkenazy's<sup>3</sup> paper illustrates the primary or direct manner of producing phlegmonous gastritis. He opened a rabbit stomach at the greater curvature and eroded the mucosa in two areas of the lesser curvature. The curette he used carried material from the floor of a human ulcer that had ruptured. Autopsy after three days revealed an extensive phlegmonous gastritis.

Of interest is another experiment by Doehle, published by Konjetzny.<sup>3</sup> Streptococcus cultures taken from the spleen and the stomach wall of a patient who had died of phlegmonous gastritis were fed to dogs. The dogs remained well. The experiment was repeated after an alcoholic gastritis was produced in the animals. This time the dogs died. Autopsy revealed a streptococcus phlegmon of the stomach with extensive edema and a fibrino-purulent peritonitis.

This experiment bears out the theory of a number of authors who consider gastritis, especially that type which is produced by alcohol, as a predisposing factor for phlegmon of the stomach (Bernstein,<sup>1</sup> Bricheteau,<sup>1</sup> Kinnicut,<sup>1</sup> Wallmann<sup>1</sup>). Sundberg<sup>1</sup> explains this by the fact that gastric mucosa which shows inflammatory changes is extremely vulnerable. According to him these cases of gastritis are in the same category as those in which a defect of the mucosa is present like carcinoma, ulcer, trauma, which acts as a portal of entry for the ingested organisms. Contini<sup>19</sup> produced phlegmons of the stomach by both the local direct and hematogenous routes, using external trauma.

Several other attempts to produce a phlegmonous gastritis were unsuccessful. Symmers<sup>20</sup> fed animals ground glass and inoculated streptococci and pneumococci by way of blood stream or stomach tube without results. Konstantinowich also failed to produce the lesion by feeding glass and streptococci to experimental animals. This might be explained by the fact that ground glass is not a good means of producing a mucosal defect, which is proved by Simmons and von Glahn.<sup>21</sup> These authors failed to produce any lesions whatsoever in dogs by repeated ingestion of ground glass.

**Bacteriology** By Gram and Giemsa stain, bacteria are found in all layers of the wall, most numerous, of course, in the submucosa, which is usually the main site of the process. In the center of small abscesses, they often form colonies and little clumps.

Since 1874 it has been known that phlegmonous gastritis is produced by bacteria. Heller<sup>1</sup> proved the presence of cocci. In 1885, Sebillon<sup>1</sup> isolated a streptococcus. In Sundberg's<sup>1</sup> cases, 95 were examined bacteriologically. Out of these, 71 cases showed streptococci. Finsterer's<sup>3</sup> statistics

show a still higher percentage, 27 out of 30 cases were positive for streptococci. They were found in pure culture or together with *B. coli* and staphylococci, rarely associated with *B. proteus*. Several cases were produced by pure cultures of pneumococci. Morton and Stabins<sup>10</sup> describe a case due to *B. Welchii*. Also anthrax-like rods, Oppler-Boas bacilli, micrococci, and *B. subtilis* were found by one author. In two patients, Stapelmohr<sup>1</sup> found the pus to be sterile. Both patients recovered. In one of Bircher's<sup>2</sup> cases also the pus was free of organisms. This case died of ruptured splenic varix, a month after successful resection of the phlegmon.

*Pathological Anatomy* The difficulty encountered with the clinical diagnosis is not found at the autopsy table. The postmortem findings are very constant and have been recognized for a long time. Cruveilhier<sup>1,3</sup> gives a detailed autopsy report in 1821 describing "purulent infiltration in the submucosa." This still is considered to be the outstanding and essential lesion. The gross findings vary a little more than do the microscopic. Although most authors describe a great increase in the width of the stomach wall (1 inch in Lehnhoff's<sup>2</sup> case, 8 to 10 centimeters in one of Bircher's<sup>2</sup> cases), a few found a thin wall of only a few millimeters. Hall and Simpson<sup>1,3</sup> report a case in which the wall was so thickened that in spite of the normal size of the stomach, the cavity was practically obliterated, and the relative size of wall and cavity resembled strikingly that of a uterus. The stomach wall may be firm and rigid, or soft and doughy, or sponge-like. In the latter case, it can be pressed together to normal thickness (Hermann<sup>1,3</sup> and Berka<sup>3</sup>). The thickening either is diffuse or regional. Walnut-like protrusions into the lumen are described by Hermann in the cases involved regionally. The pyloric area most often shows the severest lesion. Sometimes the phlegmonous inflammation extends to the esophagus (Zenker,<sup>1,3</sup> Chwostek,<sup>1</sup> Pfister,<sup>1,3</sup> Schnarrwyler<sup>1,3</sup>). The duodenum is involved very rarely. Increase in width of the wall is caused mainly by the swelling of the submucosa, whereas grossly the other layers of the wall differ little or not at all from normal.

*Symptomatology* Though there exists quite an extensive literature, and the disease has been known for many hundreds of years, phlegmonous gastritis is as yet very rarely diagnosed ante mortem. By going through the published papers, one gets the impression that the correct clinical diagnosis decreases in frequency as time goes on. It seems that phlegmonous gastritis can be diagnosed only by careful history and examination, and that blood chemistry, roentgen-ray, etc., are of little or no value. Berg<sup>5</sup> in "Roentgenuntersuchungen am inneren Relief des Verdauungskanal" points out that "only in very rare instances would phlegmonous gastritis become the subject of roentgen-ray investigation, and only if the course happened to be of more or less subacute character." The authors found very few papers in which roentgen-ray is suggested for diagnosing the ailment (Cutler and Harrison,<sup>6</sup> Watson,<sup>7</sup> Olsson<sup>8</sup>). The last writer states that "extensive thickening of the stomach wall with relatively insignificant changes in the mucosa suggest

phlegmonous gastritis " In Vass and Sirca's<sup>9</sup> case the lesion could not be diagnosed roentgenologically The symptoms that led some authors to make the correct diagnosis were very acute onset of complaints such as lack of appetite, headache, nausea, severe abdominal pain either diffuse or localized in the epigastrium and left hypochondrium or even in the right hypochondrium (Barnett and Harris<sup>10</sup>) In rare cases complaints pointing to a stomach ailment were completely absent (André<sup>3</sup> and Cruveilhier,<sup>1,3</sup> E. Krause,<sup>11</sup> and others) Vomiting is probably the most constant finding of all The temperature is high from the very onset, being either continuously elevated or septic in character, but is also described as normal or even subnormal (Marshall<sup>12</sup>) The pulse is frequent, weak and irregular The patient appears severely sick, sometimes excited, apprehensive or lethargic Hiccough is frequently present

On palpation of the abdomen severe tenderness and "defense musculaire," especially of the upper abdomen, are noted by many observers In some cases a tumor-like protusion in the region of the stomach was found which, according to a few authors, disappeared after vomiting of a purulent material In reviewing the literature, vomiting of purulent material was not found to be a frequent occurrence by any means In the vast majority of published cases, no pus was present in the stomach contents Still rarer is the finding of blood, or of a mixture of blood and pus in the vomitus Dryness and coating of tongue have been observed rather frequently In the cases collected by Sundberg, all those studied showed hypoacidity Icterus, leukocytosis, splenic enlargement, albuminuria, streptococci in the feces, and blood are mentioned in a number of reports

Of great interest is a symptom which was first described by Deininger<sup>1</sup> in 1879, later mentioned by Kermauner,<sup>1,3</sup> Bossart,<sup>1,3</sup> finally by Sundberg,<sup>1</sup> E. Krause,<sup>11</sup> and Cutler and Harrison<sup>6</sup> They observed that spontaneous abdominal pain disappears on sitting up and reappears on lying down again

Peritonitis is a frequent feature Robertson<sup>1</sup> found peritonitis in 70 per cent of his cases, Sundberg<sup>1</sup> in 65 per cent and Jensen<sup>1,3</sup> in 50 per cent Pleuritis is much less frequent According to Lengemann<sup>1</sup> 10 per cent of the patients showed pleural involvement, and according to Sundberg<sup>1</sup> 15 per cent presented this finding

Whether spontaneous recovery does occur is subject to much discussion Although the French authors Petit-Dutailis,<sup>13</sup> Cheimisse,<sup>1,3</sup> etc., are convinced that cases of diffuse phlegmon of the stomach never get cured spontaneously, Stapelmohr<sup>1</sup> describes a case of spontaneous recovery Lengemann's,<sup>1</sup> and one of Bircher's<sup>2</sup> patients also recovered Kaufmann,<sup>1</sup> Bossart,<sup>1,3</sup> Sundberg<sup>1</sup> and Gerster<sup>2</sup> believe that a spontaneous cure can occur

That a phlegmonous gastritis can heal by operative intervention has been recently shown in a number of cases (Orator,<sup>2</sup> Novak, Guibal,<sup>2</sup> Brooks and Clinton,<sup>2</sup> Cutler and Harrison,<sup>6</sup> etc.)

From the above it is clear that there is nothing pathognomonic or even characteristic in the signs and symptoms of phlegmonous gastritis. This makes the diagnosis extremely difficult. Few cases are known in the literature in which the diagnosis was made clinically and verified by postmortem examination.

### SUMMARY AND CONCLUSION

Three cases of phlegmonous gastritis are presented, showing no mucosal defect in the form of ulcer, neoplasm or operative wound. Marked dilatation of the stomach was an interesting roentgenological observation in one of them.

One case of marked edema of the stomach submucosa in a case of meningococcemia with early meningitis is presented as an early manifestation of a phlegmonous inflammation of the stomach.

Phlegmonous gastritis is compared with phlegmonous cholecystitis. A case demonstrating such phlegmonous inflammation in the gall-bladder wall in a case of known sepsis is presented.

Phlegmonous gastritis is considered a manifestation of sepsis with localization in the stomach wall rather than a lesion following local invasion from the lumen.

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# ACUTE PLASMA CELL LEUKEMIA<sup>3</sup>

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THE term "plasma cell" has been applied to a variety of cells since it was first introduced by Waldeyer in 1875<sup>1</sup>. The morphology of the cells was subsequently described in detail by Cajal,<sup>2</sup> Unna,<sup>3</sup> and von Marschalko.<sup>4</sup> These authors presented the characteristics and criteria by which they could be identified. Since these earliest descriptions the literature on these cells has become large and controversial. Papers by Michels<sup>5</sup> and Maximow<sup>6</sup> contain the most complete discussions. The cells are found under normal conditions in the omentum, interstitial tissue of glands, lymph nodes and bone marrow. In pathological states they are found in areas of inflammation (granulomas and perivascular infiltrations) and as new growths.

Under exceptional conditions plasma cells are found in the circulating blood, e g , measles<sup>7</sup>, Hodgkin's disease<sup>8</sup>, metastatic carcinoma to bones<sup>8</sup>, myeloid leukemia<sup>7</sup>, multiple myeloma<sup>10</sup>, plasma cell leukemia<sup>11</sup>, gonococcus infections<sup>12</sup>, and infectious mononucleosis<sup>13</sup>. The histogenesis of these cells is obscure and they have been variously described as originating from lymphocytes, reticulum cells of lymphoid tissue, adventitial cells of blood vessels and myeloid cells. Jordan<sup>14</sup> strongly advocates the theory that they are abortive erythroblasts. The preponderance of evidence seems to point to the lymphocytes as the probable source of these cells. Naegeli<sup>7</sup> is so convinced of the origin of the plasma cells that he calls them lymphocytes with strongly basophilic cytoplasm. The fate and function of the plasma cell are uncertain, but it has been suggested that they may be converted into connective tissue or back to lymphocytes.

In a consideration of new growths involving plasma cells the solitary extra-medullary plasmacytomas with and without subsequent involvement of distant organs or bone marrow constitute a distinct and separate group. They are most commonly found in the nasopharynx,<sup>15</sup> and to a lesser extent in the conjunctiva, lymph nodes and other sites<sup>16</sup>. These tumors may run either a benign or a malignant course. A recent review by Hellwig<sup>10</sup> brings this entire subject up to date. There is also a small group of cases of single plasma cell tumors originating in the bone marrow. Some of these cases are apparently benign, the patient showing no evidence of disease after extirpation of the tumor<sup>17, 18, 19, 20</sup>. Other cases recur locally or manifest distant metastases<sup>15</sup>.

Multiple myeloma is the most frequent disease involving new growths of plasma cells. The first case of multiple myeloma was described in 1850

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by McIntyre<sup>21</sup> It was in the urine of this patient that Bence-Jones<sup>22</sup> found a peculiar protein which he reported in 1848 Von Rustizky<sup>23</sup> in 1873 was the first to describe these tumors in detail and to identify the plasmacyte as the invading cell A complete review of the literature and detailed descriptions of the disease were made by Geschickter and Copeland<sup>24</sup> who reported a total of 425 cases up to that year (1928) In these cases the infiltrating cell was described as a plasma cell Ulrich<sup>25</sup> in 1939 and Ghormley<sup>26</sup> in 1942 bring the subject up to date and discuss the existence of a specific "myeloma cell" versus the plasma cell Ewing<sup>15</sup> states that although the tumors generally consist of plasma cells, there are also cases which are made up of myelocytes, lymphocytes and erythroblasts The classical picture of multiple myeloma is that of a diffuse involvement of ribs, sternum, vertebrae, skull, pelvis and humerus in a neoplastic growth arising in the bone marrow with resulting nodule formation There are also cases reported in which there is extensive distant organ involvement, but to a lesser extent than is usually seen in leukemia Included in this group are those cases of multiple myeloma in which plasma cells have been found in the circulating blood The first case showing this phenomenon was reported by Foa<sup>27</sup> in 1903 Aschoff<sup>28</sup> in 1906 found plasma cells in the blood of a case of multiple myeloma on which he was performing an autopsy Since these two reports a series of cases has been reported, these cases are recorded in table 1

Finally there is a small group of cases in which the patients run the clinical course of leukemia showing diffuse organ and bone marrow invasion by plasma cells but no apparent bone marrow nodule formation In these cases plasma cells were also noted in the circulating blood Piney<sup>12</sup> described the case of a man, age 48, who complained of weakness in the legs, with pain in the legs and lumbar region A large spleen was present An enlarged cervical node was excised and showed an overgrowth of plasma cells Albumin but no Bence-Jones protein was found in the urine The white cells varied from 8,400 to 20,000/cu mm with 18 to 55 per cent plasma cells The clinical course of the patient is not given and no skeletal roentgen-rays were taken At autopsy the spleen was described as enlarged but weighed only 185 gm The bone marrow of the ribs, upper femur and vertebrae were described as having decreased consistency The histological sections of liver, spleen, lymph nodes, kidneys and bone marrow showed a widespread invasion of plasma cells, similar to that seen in leukemia Piney excluded a diagnosis of multiple myeloma because of absence of Bence-Jones protein in urine, the diffuseness of infiltrations in the organs, and the absence of tumor masses in the bones at autopsy It is difficult for the present authors to accept this case as not being one of probable multiple myeloma The absence of Bence-Jones protein in the urine is of no consequence as not infrequently it is not found,<sup>29</sup> particularly where hyperproteinemia exists Furthermore, no roentgen-ray studies were taken during life The diffuse infiltration of plasma cells in the organs does not militate against a diagnosis

TABLE I

Reported Cases of Multiple Myeloma with Plasma Cells in the Circulating Blood

			References
Foa	1904	Plasma cells in smears	Folia haemat Abstracts, 1904, i, 166
Aschoff	1906	Plasma cells found in post-mortem smears	Munchen med Wchnschr, 1906, liii, 337
Gluzinski and Reichenstein	1906	77% plasma cells	Wien klin Wchnschr, 1906, xix, 336
Luksch	1906	Many plasma cells	Folia haemat, 1906, iii, 325
Amersbach and Schriddle	1912	Plasma cells in smears	Quoted by Vogt Frankf Ztschr f Path, 1912, x, 129
Ghon and Roman	1913	15% plasma cells	Folia haemat, 1913, xv, 72
Hertz and Mamrot	1913	5% plasma cells	Folia haemat, 1913, xvi, 227
Beck and McLeary	1919	6.6% plasma cells	Jr Am Med Assoc, 1919, lxxii, 480
Weinberg and Schwartz	1920	Plasma cells in smears	Virchow's Arch f path Anat u Physiol, 1920, ccxxvii, 88
Wallgren	1920	Case 4-8% plasma cells	Upsala Lakaref Forh, 1920, xxv, 113
Piney and Riach	1931	16 to 33% plasma cells	Folia haemat, 1931, xlvii, 37
Muller and McNaughton	1931	Case 1-39 to 53% plasma cells Case 2-65% plasma cells	Folia haemat, 1931, xlviii, 17
Cabot Case 21052	1935	5 to 15% plasma cells	New England Jr Med, 1935, ccxii, 204
Patek and Castle	1936	12 to 33% plasma cells	Am Jr Med Sci, 1936, cxcii, 788
Jores and Bruns	1936	42% plasma cells	Folia haemat, 1936, lv, 227
Fleischhacher and Klima	1936	Case 4-0 c c plasma cell Case 10-13% plasma cells	Folia haemat, 1936, lvi, 5
Schilling and Wohlenberg	1938	Few plasma cells	Munchen med Wchnschr, 1938, lxxxv, 1292
Lochnit and Walterskirchen	1939	53 to 71% plasma cells	Wien klin Wchnschr, 1939, lii, 67
Lemaire, Urey, et al	1940	46% plasma cells	Bull et mém Soc med d hôp de Paris, 1940, lv, 1366
Ulrich	1939	0 to 10% plasma cells	Arch Int Med, 1939, lxiiv, 994
Rubin	1942	Case 1-38 to 54% plasma cells Case 2-1 to 4% plasma cells	Bull Hosp Joint Dis, 1942, iii, 62
Ashkanazy and Dubois Ferriere	1942	77 to 93% plasma cells	Helvet med acta, 1942, ix, 427

of multiple myeloma as this disseminated process has been described<sup>15, 24, 25</sup> and is prominently seen in cases listed in table 1

Jackson, Parker and Bethea<sup>30</sup> (case 5) describe a patient, male adult, age 51, who was admitted to the hospital with the complaints of fatigue, bloating and pain in the legs. The spleen and inguinal nodes were enlarged. There was "moderate elevation" of white blood cells, of which 65 per cent were plasma cells. There were also lymphocytes which were difficult to classify. No bone marrow studies or skeletal roentgen-rays were done. Irradiation of the spleen resulted in reduction in the size of this organ. One year later symptoms returned and the spleen again became enlarged. It became smaller following roentgen-ray treatment. "The blood continued to show typical plasma cells and atypical lymphocytes." Eight months later the blood became normal, the spleen remained enlarged and lymphadenopathy was generalized. Biopsy of two inguinal nodes showed no pathological changes. In a discussion of this case the authors state no bone lesions were demonstrated. No subsequent information is available as this patient failed to return for further care.<sup>31</sup> This patient has obviously been inadequately studied and without any follow-up cannot be accepted as a case of plasma cell leukemia. The absence of skeletal roentgen-ray studies and the negative reports of inguinal node biopsies sustain this position.

In 1934 Osgood and Hunter<sup>32</sup> reported the case of a man, aged 49, whose chief complaints were nosebleeds and weakness. The total duration of this patient's illness was six weeks. The patient was markedly anemic. There was hemorrhage from the nose, a gum infection was present, and the breath had a foul odor. The spleen, axillary and inguinal nodes were slightly enlarged. The white cells varied from 15,700 to 34,050 with plasma cells ranging from 47-54 per cent. Bence-Jones protein was absent from the urine. The blood proteins were 8.79 gm, albumin 1.56, and globulin 6.94 gm. Roentgen-ray studies showed "findings in the skull suggestive of changes found in parathyroid disease. Lues and Paget's disease are also to be considered. The long bones, pelvis and ribs failed to demonstrate any radiographic evidence of pathology." There is no report of any studies on the spine. The patient's course was short in the hospital, during this time he developed petechiae, bleeding gums, epistaxis and otitis media. Autopsy was limited to the abdomen. The liver, spleen and lymph nodes were enlarged and showed widespread infiltrations with plasma cells. The bone marrow was similarly involved. The ribs and sternum were examined with difficulty through the diaphragm and no nodules were felt. The authors excluded a diagnosis of multiple myeloma because of absence of Bence-Jones protein from the urine, absence of bone pain and absence of bone changes. The absence of Bence-Jones protein in the urine has been discussed in the case reported by Piney<sup>12</sup> and is, therefore, of no significance. The authors apparently disregard the roentgen-ray description (quoted above) of the skull, which strongly suggests multiple myeloma. Since the autopsy was limited to the abdomen, tumor nodules might have been present

in the marrow of the ribs or sternum and obscured by a thin layer of cortex. Sections of the skull would have been most desirable before excluding a diagnosis of multiple myeloma.

In 1937 Reiter and Freeman<sup>23</sup> reported the case of a woman, age 66, who complained of weakness and paresthesias of four months' duration. The patient had been treated for six months with liver extract, a diagnosis of pernicious anemia having been made. There was no improvement clinically on this therapy. 'Physical examination was entirely negative.' During the patient's stay in the hospital she manifested great weakness. The total white cells varied from 5,200 to 7,000 with 39 to 48 per cent lymphocytes and 1-8 per cent monocytes. There were no roentgen-rays reported and no diagnosis was given in the paper. At autopsy no skeletal masses were found. No enlarged nodes, spleen or liver were described. The skull was not mentioned. Histological study showed an overgrowth of the lymph nodes, spleen and bone marrow by plasma cells. A differential count was done on the cells in the vessels of the liver and pancreas, and this disclosed 72 to 74 per cent plasma cells. The authors concluded that the blood smears during life were misinterpreted and that the so-called lymphocytes were most probably plasma cells. The same criticism must be applied to this case as was mentioned in those described by Piney<sup>12</sup> and by Jackson,<sup>20</sup> since no roentgen-ray studies were made during life.

The cases listed in table 1 are obvious cases of multiple myeloma with plasma cells in the peripheral blood. The second group described in detail (Piney, Jackson et al., Osgood and Hunter, Reiter and Freeman) probably fall into the same group for the reasons listed in the description of each case. The present authors therefore present the following case which they feel fulfills all the criteria of an acute leukemia.

TABLE II  
Cases Reported as Plasma Cell Leukemia

Piney <sup>12</sup>	1924	18 to 55% plasma cells
Jackson, Parker and Bethca <sup>25</sup>	1931	65% plasma cells
Osgood and Hunter <sup>23</sup>	1934	47 to 54% plasma cells
Reiter and Freeman <sup>21</sup>	1937	72 to 74% plasma cells

#### CASE REPORT

W. B., white female, age 67, was admitted to the Kings County Hospital on April 30, 1943, with the chief complaints of pain across the chest and swelling of feet and legs. Patient had dropsy at the age of six and since she was 35 years of age there were numerous attacks of dependent edema and dyspnea. For four weeks prior to admission the patient had had severe frontal headaches, dizziness and periods of unconsciousness. During this period she lost nine pounds and occasionally coughed up a little blood. The positive physical findings on examination were the apparent severe anemia, ptosis of the left eyelid, enlarged cervical and inguinal nodes, and the presence of a round mass in the right iliac region which was movable and painful on pressure. Temperature was 100.2° F, pulse 100, blood pressure 120 mm Hg systolic and 60 mm diastolic. Urinalysis disclosed albumin 3 plus with many hyaline casts and white blood cells. The initial and subsequent blood counts are shown in table 3.

TABLE III  
Peripheral Blood

Date	Hb	RBC	WBC	Seg PMN	Non Seg PMN	Mycocytes	Lymphocytes	Monoocytes	Plasma Cells
5/6/43	55%	2,140,000	31,000	30%	6%	2%	11%	7%	44%
5/11/43	50%	2,450,000	15,000	49%	31%	4%	11%		5%
5/13/43			11,000	64%	11%		9%	13%	3%

Further laboratory examination made during the first 48 hours in the hospital showed Urea 58 mg per cent, sugar 82 mg per cent; creatinine 14 mg per cent. Prothrombin time was 75 per cent of normal. Urinary urobilinogen was 4 plus. Bence-Jones protein was absent from the urine. The total proteins of the blood were found to be 11.0 gm per cent of which 2.5 gm were albumin and 8.5 gm globulin. Blood Wassermann reaction was negative. Sternal puncture was done on several occasions and the results are noted in table 4.<sup>34</sup> Three days after admission the

TABLE IV  
Bone Marrow Studies

Date	Total Nucleated Cells	Megakaryocytes	Seg PMN	Non Seg PMN	Myelocytes	Myeloblasts	Plasma Cells	Lymphocytes	Megakaryoblasts	Erythroblasts	Normoblasts
5/6/43	32,000	0	27%	7%	6%	0	48%	8%	0	0	4%
5/8/43	45,000	0	7%	4%	8%	1%	27%	4%	0	0	49%
5/11/43	250,000	22	13%	8%	6%	0	30%	4%	0	1%	38%
5/13/43	175,000	0	4%	5%	16%	1%	31%	3%	1%	3%	36%

patient developed signs of bronchopneumonia at both bases and sulfathiazole therapy was instituted. The highest blood level reached was 3.8 mg per cent. During the entire course in the hospital the patient was drowsy and slept most of the time. A lumbar puncture five days after admission revealed no abnormalities. On the sixth day the patient complained of pain in the abdomen and passed a yellow watery stool. She was obviously icteric. The gums were oozing and swollen. Purpuric spots were found over the body. The axillary nodes were now enlarged in addition to the cervical and inguinal. The signs of consolidation became more marked at the right base. This was confirmed on roentgen-ray of the chest. The patient was given three transfusions of 500 cc each, but died 18 days after admission to the hospital. Complete skeletal roentgen-rays were taken but no abnormal bone changes were found.

The cells designated as plasma cells in the peripheral blood and bone marrow were of several types. Many were typical, being slightly larger than the lymphocyte, having a deep blue cytoplasm with a clear zone opposite the eccentrically placed nucleus. Some of the nuclei had the typical cartwheel structure, others showed a thick dense irregular chromatin (figure 1). There were other cells which were slightly larger, the cytoplasm varying from pink to bluish-gray, and a slightly larger nucleus also eccentrically placed. These cells resembled atypical normoblasts and erythroblasts. The nuclei of these cells resembled those of the typical plasma cell (figures 3 a and b). Finally there were some cells which were two to three times the size of the usual lymphocytes. The nuclei of these cells were large, occasionally oval but usually round, and finely granular. One to three nucleoli were present. The cytoplasm was of a deep blue color and had a thin clear peri-nuclear zone. These

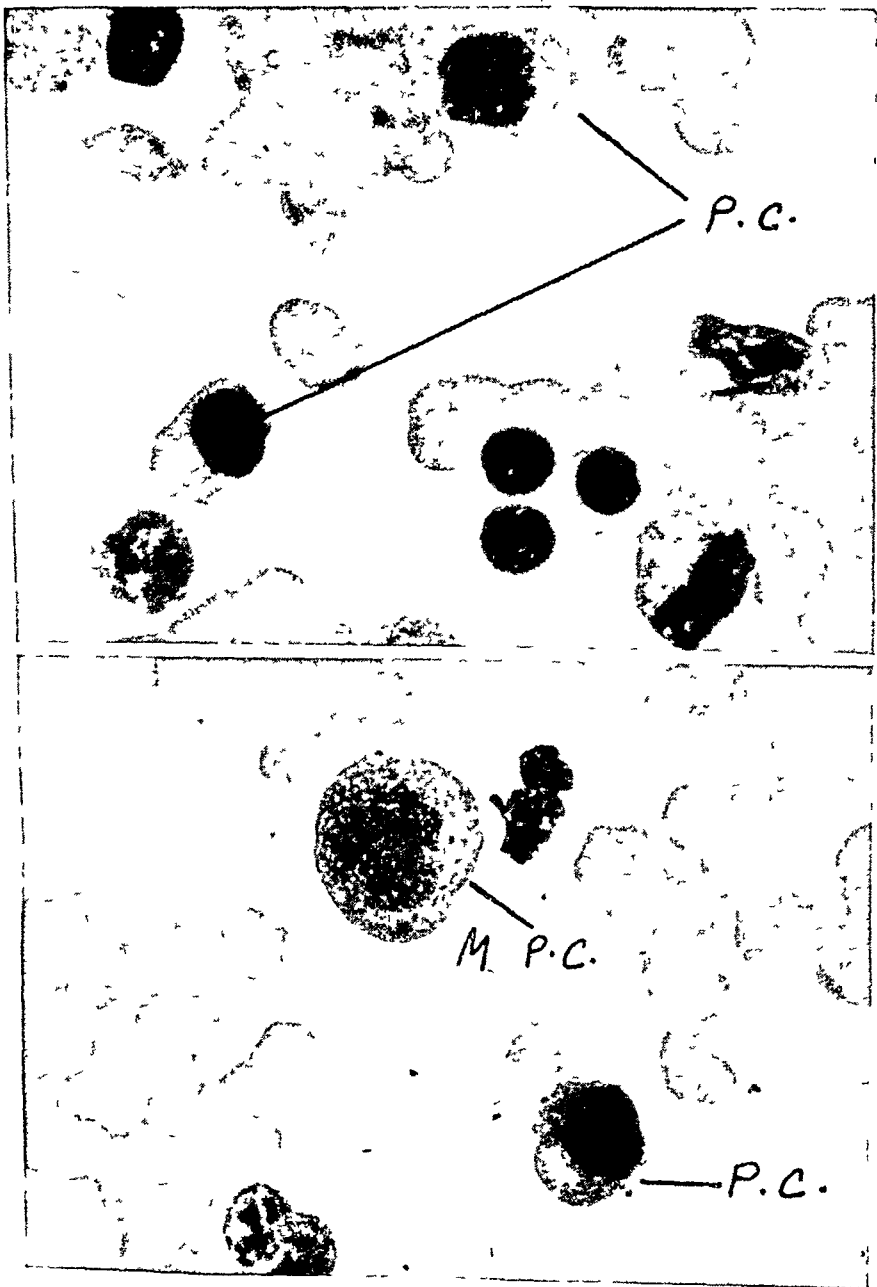


FIG 1 (above) Antemortem bone marrow smear showing typical plasma cells (P.C.)  $\times 1000$

FIG 2 (below) Megakaryoblastic type of plasma cell (M.P.C.)  $\times 1000$

cells were interpreted as being immature plasma cells and resembling closely megakaryoblasts (figure 2)

**Autopsy Description** The body was that of a well developed, poorly nourished elderly adult female, 5 feet 2 inches in height and weighing about 120 pounds. In the left cervical region there was a hard mass, about the size of a lemon. There was bilateral axillary and deep inguinal adenopathy, the nodes being discrete, and about



the size of walnuts. The body was waxy-white in color. There were varicosities of both legs. There was dependent lividity, with no jaundice, edema or operative scars, and no external evidence of recent injury. There was normal hair distribution and normal postmenopausal external genitalia. *Incision* The usual "Y" shaped incision was made, and the sternal plate was lifted in the usual manner. *Body cavities* Immediately beneath the sternum there was a large antemortem blood clot. There were no pleural adhesions, and no free fluid in the pleural cavity. There was no abdominal fluid, and the serosal surfaces of the abdominal viscera were smooth and glistening. The deep inguinal lymph nodes were enlarged to the size of walnuts and were discrete. *Head* The scalp was incised and reflected. The tissues of the sub-galea were slightly edematous, and presented many roughly circular hemorrhagic areas measuring approximately 4 mm in diameter. The calvarium was removed. The dura was slightly adherent, especially along the sagittal sinus. Several granulations were noted here. Transillumination of the calvarium showed no rarefied areas. The dura was incised and the brain exposed. Marked subarachnoid edema fluid was noted. This occupied the convex surface of the entire hemisphere. Puncture of the pia-arachnoid released considerable fluid. There was moderate to marked cerebral atrophy, as evidenced by widened and deep sulci. The brain was removed and examined. No areas of softening were noted. The vessels of the base were normally constituted, but the site of marked atherosclerosis. Serial section of midportion showed no gross pathologic lesion of the cerebellum. Horizontal section of both hemispheres revealed small cysts, which occupied the nuclei of the base. No other abnormality was visualized. *Lungs* The right lung weighed 660 grams, the left lung 650 grams. There were small hard white areas in the apices of both lungs. The surfaces of both lungs were gray-blue in color, and they both had increased resistance centrally, while the periphery was spongy. Cut surfaces revealed the lungs to be gray in color, edematous, and well aerated. There was marked hilar adenopathy. *Heart* The heart weighed 260 grams. It lay free in the pericardial cavity, and there was no free pericardial fluid. There was normal distribution of epicardial fat. The myocardium was of normal thickness, but the papillary muscles were moderately effaced. The valve surfaces were smooth, and chordae tendineae were not thickened. The ostia of the coronary arteries were patent, the vessels were traced throughout their course, and showed no obstruction or thickening of the walls. The aorta showed generalized, raised yellow plaques and had some ulcers. The wall was thin. The ostia of all branches were patent. There was calcification at the bifurcation. *Liver* The liver weighed 2,030 grams. It was enlarged to four fingers below the costal margin. The edges were sharp. The surface was smooth and friable, and gave the appearance of red and yellow streaked marble. Cut section revealed this streaking to stand out more markedly, the yellow being homogeneous. The hepatic vessels and ducts were grossly normal. The gall-bladder contained 20 cc of dark green bile. Two small black calculi were present. The mucosa was thickened, the bile ducts were patent, and pressure on the gall-bladder caused bile to flow at the ampulla of Vater. *Spleen* The spleen was enlarged and weighed 600 grams. It was soft and boggy. Several hard areas were palpable. It was grayish-red in color. The cut surfaces were boggy, and showed an increase in the gray pulp. There were black nodules present, which corresponded to the hard areas felt on the surface. *Adrenals* The adrenals were normal in position and size. Their surfaces were yellow, and cut sections revealed a yellow cortex and brown liquefied medulla. *Kidneys* The kidneys were small, and will be described together. Each weighed 160 grams. The surfaces were maroon in color, firm in consistency, and smooth in texture. The capsules were stripped with ease. Cut surfaces revealed cortex and medulla to be well demarcated, and the normal relationship existing between the two. The calyces, pelves and ureters showed no gross abnormality. The bladder contained 80 cc of cloudy yellow urine. The trabeculae

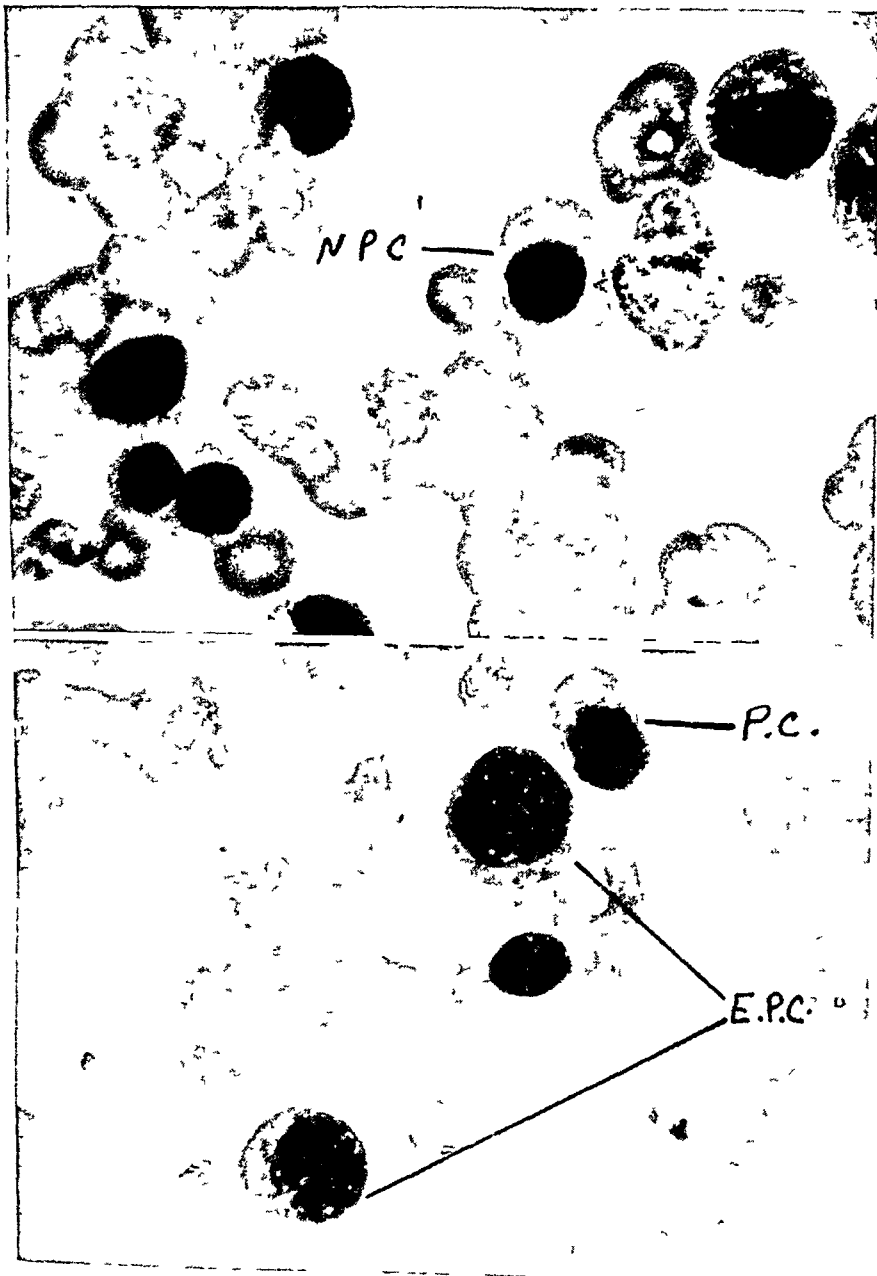
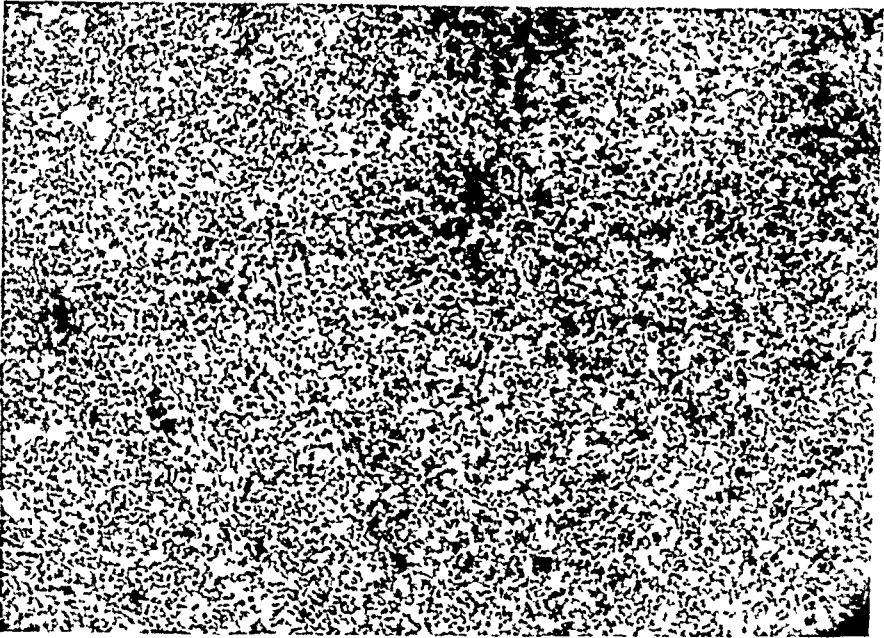
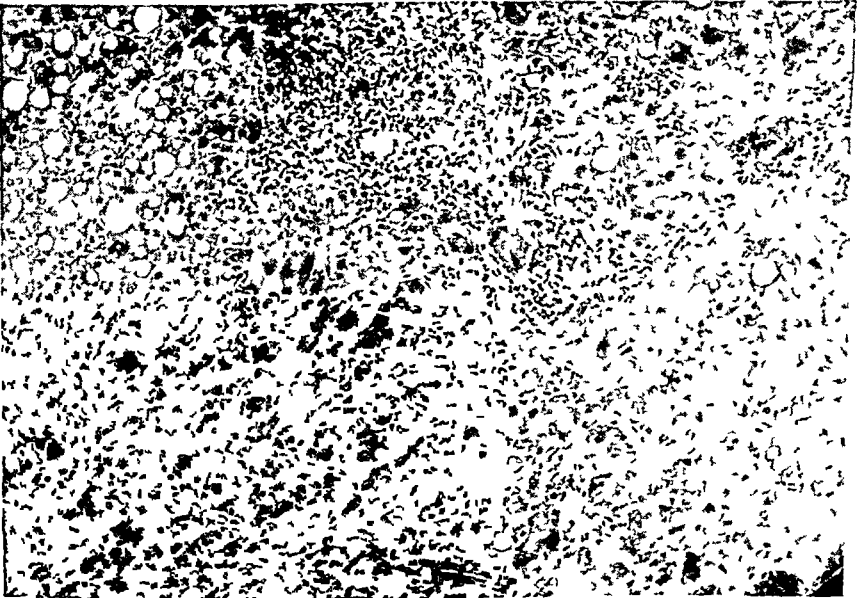


Fig 3a (above) Normoblastic type of plasma cells (NPC)  $\times 1000$   
 Fig 3b (below) Erythroblastic type of plasma cell (EPC)  $\times 1000$

were normal in size, and the mucosa was injected. *Genitalia* The ovaries were atrophic. The tubes were patent, and their fimbriated ends lay free in the abdominal cavity. The uterus was small and hard. The cervical canal was patent and its mucosa showed no gross abnormality. The mucosa of the fundus was dark red in color. There were no new growths that stood out from the surface of the mucosa. *G I Tract* The esophagus showed no dilatation, varices, or diverticulum. The mucosa was smooth and black in color, probably from postmortem autolysis. The stomach contained 100 c.c. of light green fluid. The mucosa was injected and the

FIG 4 Spleen  $\times 120$ 

rugae were atrophic. There was no ulceration or growths. The duodenum, jejunum and ileum were empty. The mucosa was injected, but there was no ulceration. There was generalized mesenteric adenopathy. There were no mesenteric thrombi or hemorrhage. The cecum, ascending, transverse, descending and sigmoid colons showed no obstruction or diverticula. The rectum was full of feces. The appendix was present and showed no gross evidence of disease.

FIG 5 Liver  $\times 120$

*Microscopic Study* (Interpretation by Dr W W Hala) *Spleen* There was a diffuse infiltration of plasma cells into the sinusoids, mixed in with the pulp cells. There were no discrete aggregations of plasma cells. The Malpighian corpuscles were indistinct and obscured. Another section of the spleen disclosed an area of hemorrhagic infarction. *Bone Marrow* Hyperplastic with an apparent increase of plasma cells. *Liver* There was an infiltration into the portal spaces and sinuses consisting of round, plasma and reticuloendothelial cells. The parenchymal cells showed evidence of extensive fatty changes (figure 5). *Lymph node* No follicles were present. The normal architecture was completely destroyed and was replaced by an overgrowth of small round and plasma cells which had infiltrated into the surrounding fat (figure 6). Imprints made of an inguinal node immediately after death demonstrated nests of plasma cells more distinctly. Most of these were typical

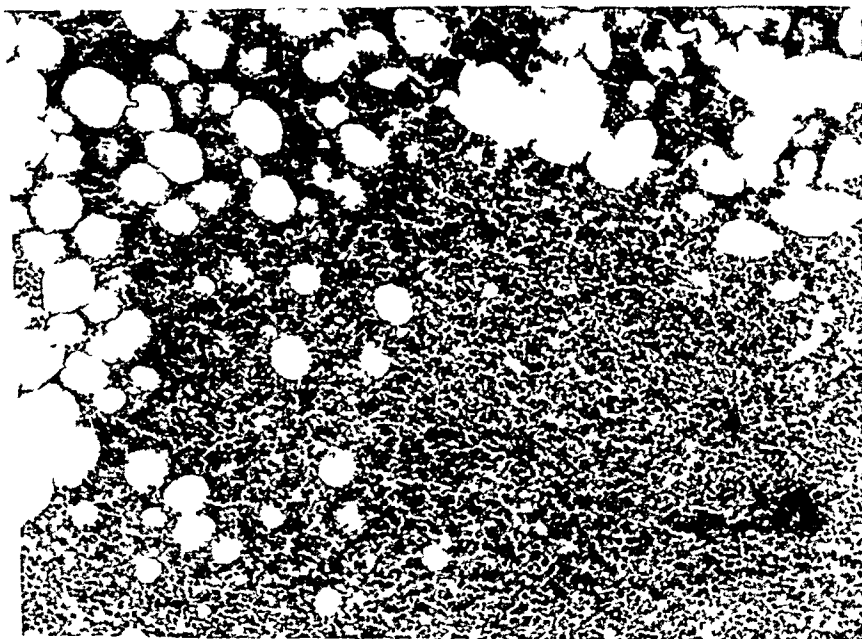


FIG 6 Lymph node  $\times 120$

plasma cells, but a few resembled normoblasts as found in the peripheral blood. The preponderance of cells, however, were lymphocytes. There was no evidence of infiltration into any of the other organs, the only pathological changes being the usual degenerative ones which are associated with senility.

### DISCUSSION

The authors do not wish to enter into the controversy as to the origin of the plasma cell. However, from the material at hand in this case, the erythroblastic theory of Jordan<sup>14</sup> finds great favor. In initial cursory examination of the marrow smears many of the cells were thought to be "atypical" megaloblasts and erythroblasts. The staining qualities of the more immature cells strongly suggested the former, and it was only after examination of many fields that the true nature of these cells was determined. Many of the older plasma cells strongly resembled normoblasts with cyto-

plasm which appeared hemoglobiniferous. At the same time the authors are aware of the overwhelming weight of such experiments as those of Maximow<sup>9</sup> who demonstrated the growth of plasma cells from lymphocytes after two days' incubation. However, the issue does become more complicated if one bears in mind the reports of Furth<sup>35</sup> who found that the intravenous injection of myeloid cells into mice produced in some instances myeloid leukemia and in other animals multiple myeloma.

The present authors have utilized the method of sternal puncture in all cases showing hematologic disorders and have found the marrow to be diffusely involved in all cases of multiple myeloma. This is in accord with the findings of Rosenthal and Vogel<sup>36</sup>. Beizer, Hall and Griffin<sup>37</sup> found only eight out of 10 cases with positive sternal marrow punctures. However, it has been the experience of one of us (L M M) in an early case of multiple myeloma that the plasma cells had a tendency to clump together in groups of six to eight and were not broken up during the process of preparing the smears. The nests of cells were so characteristic when seen that the diagnosis was made even though the smears did not show diffuse overgrowth of the cells and was later confirmed on roentgen-ray studies of the bones. This suggests that with the greater use of sternal puncture as a routine measure in obscure cases, particularly of anemias of unknown origin, the number of recognized cases of multiple myeloma will increase.

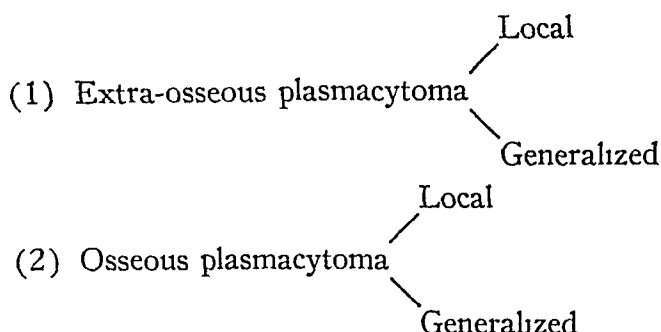
The cases of multiple myeloma with plasma cells in the circulating blood bear a strong analogy to patients with lymphosarcoma who show lymphosarcoma cells in the peripheral blood, as reported by Isaacs,<sup>38</sup> and to cases of leukosarcoma originally described by Sternberg<sup>39</sup>. Similarly, patients with lymphatic and myelogenous leukemia often show asymptomatic single and multiple localized bone lesions if routine roentgen-ray studies are done<sup>40, 41</sup>. Another close analogy is to cases of chloroma where both intra- and extra-osseous green tumors occur in conjunction with the blood picture of leukemia.

Another interesting associated finding was the elevated blood proteins with the globulin reaching a level of 8.5 grams per 100 cc of blood. This neither militates against nor confirms the diagnosis of multiple myeloma or plasma cell leukemia since hyperproteinemia is present in other diseases (notably cirrhosis of liver, lymphogranuloma venereum and kala-azar<sup>42</sup> and may be absent in myelomatous disease (especially where Bence-Jones protein is found in the urine<sup>29</sup>).

As far back as 1907 Pappenheim<sup>43</sup> suggested that multiple myeloma is a generalized disease of the hematopoietic tissue which happens to affect at first or primarily the bone marrow. Since that date numerous authors have stressed the relationship of diffuse multiple myeloma to the lymphatic and myelogenous leukemias. This becomes even more apparent when patients with diffuse myelomatous tumors begin to show plasma (myeloma?) cells in the circulating blood, as recorded in table 1. The present case reported completes the chain in the analogy to lymphoid tumors in that no masses

were demonstrated in any bone either by complete skeletal roentgen-rays or after a careful search at the autopsy table. The diffuse invasion of organs, including lymph nodes and bone marrow with the presence of immature and mature plasma cells in the circulating blood justifies the designation in this case of acute plasma cell leukemia.

The classification of tumors involving plasma cells which has been suggested by several authors (Naegeli,<sup>7</sup> Jackson et al,<sup>30</sup> Muller and McNaughton (table 1), and Ulrich<sup>25</sup>) may be combined into the following simple but comprehensive form



#### SUMMARY AND CONCLUSION

1 A case of acute plasma cell leukemia is presented which fulfills all the clinical and hematological criteria necessary for the diagnosis of acute leukemia.

2 The elevated blood globulin in association with overgrowth of plasma cells in organs, bone marrow and peripheral blood indicates the close relationship of this case to diffuse multiple myelomatosis.

3 A review of the literature of various plasma cell neoplasms suggests that they are all part of the same disease process involving hematopoietic tissues and organs. The above case completes this chain.

4 A condensed and comprehensive outline of plasma cell tumors is presented.

5 From the material at hand in this case it is suggested that some plasma cells are developed from abortive megaloblasts or their derivatives.

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# CASE REPORTS

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## AN UNUSUAL CASE OF AORTIC ANEURYSM<sup>\*</sup>

By S P SANFORD, M D, *Savannah, Georgia*

ON October 13, 1939, a negro male, age 18, who gave the date of his birth as June 3, 1921, was admitted to the hospital with primary syphilis. His history revealed that his father, age 45, was living and well, and that his mother died at the age of 30, cause unknown. Four siblings are living and well. The patient was single. He had had measles in childhood, mumps at eight, chickenpox at 10, and malarial fever at 13.

His present illness had begun about three weeks before admission with a penile ulcer and generalized pustular eruption over the body. There was no itching. There had been no noticeable loss of appetite. There had been a feeling of feverishness intermittently for two weeks.

Physical examination revealed a young negro male with good musculature. There was a healing ulcer in the coronal sulcus that was definitely indurated. The epitrochlear and inguinal lymph nodes were definitely enlarged. One inguinal node was rather large and painful. The body was covered by numerous pustules. The rest of his physical examination was normal.

A dark-field examination of the ulcer showed spirochetes of syphilis. The Wassermann reaction was strongly positive, and the Kahn reaction was strongly positive, 240 units. The blood examination was as follows: red blood corpuscles, 3,800,000, white blood corpuscles, 5,000, hemoglobin, 50 per cent, differential count: small mononuclears 26 per cent, large mononuclears 1 per cent, and neutrophils 73 per cent. Feces showed ova of *Trichuris trichiura*.

The patient was treated with neosalvarsan, 0.3 gram initial dose, followed at weekly intervals by 0.6 gram for eight doses. He was also given concurrently eight doses of thio-bismol 0.2 gram each. A spinal fluid examination was made on October 25, which was reported as follows: Albumin normal. Cell count 1. Globulin negative. Mastic 000000. The intestinal parasites were apparently removed by tetraethylene M60 successfully as subsequent examination showed no ova.

The serological tests for syphilis made at the conclusion of the first course of treatment were as follows: Wassermann reaction, four plus. Kahn reaction, four plus, units 10. The patient did not return for a second course.

On July 24, 1941, approximately two years after initial infection, the patient returned to this hospital complaining of severe pains over his heart. These, he stated, had begun three weeks previously while he was employed as a shrimp fisherman. He had had paroxysmal nocturnal dyspnea. He had had a slight fever for six weeks, but no other symptoms were elicited on careful questioning.

Physical examination at this time revealed a well developed muscular negro male of 20 years, weight 138 pounds, height 5 feet, 6 inches.

The pupils were small, equal and active. The alignment and development of the teeth were excellent, the throat was normal. The neck showed marked pulsations in both carotid regions and in the region of the right subclavian artery. The thorax was well covered, and there were no other pulsations noted by direct and tangential inspection. The heart rate was 90 and the rhythm regular. The apex impulse was

<sup>\*</sup> Received for publication July 26, 1943.

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not sharply localized. The sounds were overactive. The aortic second sound was accentuated, low pitched and followed immediately by a murmur. His blood pressure was 120 mm Hg systolic and 60 mm diastolic, the same in both arms. The aorta was easily felt in the jugular notch. The peripheral arteries were not sclerosed, and there were no varicosities. Duroziez's sign was not elicited. The lungs were clear. The abdomen was negative. The spleen was not palpable. The cervical, axillary, epitrochlear, and inguinal lymph nodes were all palpable. The urinalysis was normal, the red blood count was 4,270,000, hemoglobin, 69 per cent. The Wassermann and Kahn tests were negative. The spinal fluid examination of August 5, 1941, was as follows: Albumin normal. Globulin negative. Cell count 8 cells per cu mm fluid. Mastic 000000. C S F Wassermann reaction—negative.

A roentgenographic examination of the chest revealed a large aneurysm of the distal portion of the aortic arch. A simultaneous electrocardiogram and stethogram

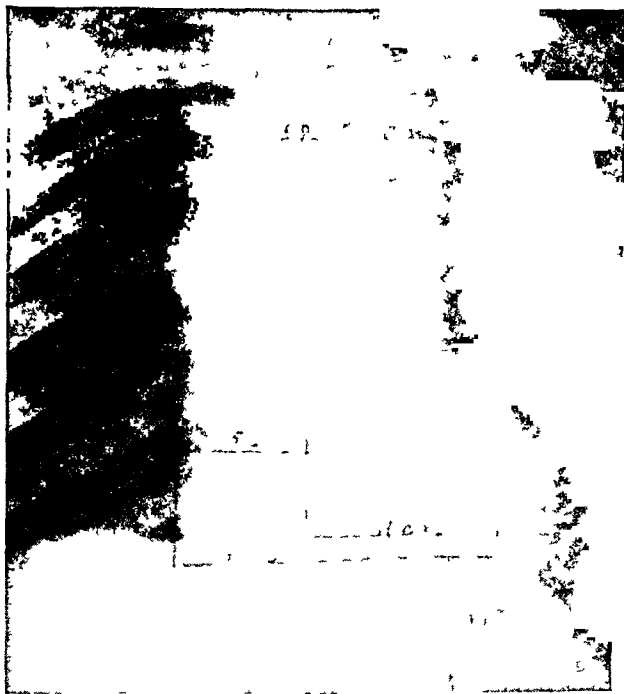


FIG 1 Roentgenogram of chest taken July 24, 1941, showing aneurysm

showed a diastolic murmur replacing the second sound. The conducting mechanism was within normal limits,  $S_1$ - $S_2$  and  $S_3$  were slurred.

A second roentgenographic examination of the aorta showed the ascending loop reduced in size. This was thought to be caused by subsidence of perivascular lymphedema. It does not seem reasonable to believe that the reduction in size represents a reduction in the caliber of the aorta.

The patient lived until December 5, 1942, when he finally succumbed to pulmonary congestion. Peripheral signs of aortic insufficiency had developed.

An autopsy revealed a saccular aneurysm almost four inches in diameter below the descending loop of the arch. The aortic valves were eroded. The rest of the thoracic aorta was involved in a syphilitic process of thickening and longitudinal striations.

In negro patients aneurysm of the aorta has not been an infrequent finding. The average age at the onset of the symptoms is considerably lower than that

for the general population. This has been attributed to widespread youthful infection and to arduous labor. It is not unusual to see negroes incapacitated by aneurysms or other forms of vascular syphilis in the early thirties, but for aneurysm to develop in a 20 year old youth, within two years of the proved initial infection, is indeed a medical curiosity.

Evans<sup>2</sup> was able to find only two cases of thoracic aneurysm in persons below the age of 30 in addition to one case which he reported. One of these cases was 29 and the other 28.

In this period of 46 years there were 840 cases of thoracic aneurysm admitted to the London Hospital.

### SUMMARY

This case of a 20 year old negro dying from an aneurysm of the aorta is unique from two standpoints. In the first place aneurysm of the aorta is extremely rare in one so young. In the second place it is very rare for an aneurysm to develop within two years of proved primary infection.

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## DISSEMINATED VISCERAL IDIOPATHIC HEMORRHAGIC SARCOMA (KAPOSI'S DISEASE) REPORT OF CASE WITH NECROPSY FINDINGS \*

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THE lesion of idiopathic hemorrhagic sarcoma (sometimes called angio-reticuloendothelioma) or Kaposi's disease, is a granulomatous tumor characterized by vascular proliferation and hyperplasia of spindle cells which are of doubtful origin<sup>1, 2, 3, 4</sup>. The fact that various theories have been advanced as to the pathogenesis of the disease is indicative of the fact that the actual nature of its origin remains obscure, although it is generally believed to represent a true neoplastic process rather than an infectious one<sup>2, 4</sup>. The disease occurs almost always in men who are manual laborers, the great majority of them being Jewish or Italian, of eastern European or northern Italian stock<sup>1, 4</sup> usually during the fifth, sixth or seventh decades of life. The course of the disease is ordinarily prolonged, lasting from six months to 25 years.

Visceral involvement associated with cutaneous lesions in Kaposi's disease is not uncommon. Disseminated visceral lesions in the absence of cutaneous manifestations is relatively unusual and, in fact, the existence of such substantiated cases has been strongly questioned<sup>1</sup>. In an extensive review of the subject

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Choisser and Ramsey<sup>1</sup> cited one instance of Kaposi's disease without skin lesions and reported two additional cases. Weller<sup>5</sup> has also described two similar cases. The purpose of this communication is to present the clinical study and necropsy findings of a patient who had no skin manifestations but who showed widespread visceral involvement by a hemorrhagic sarcoma the histological picture of which conformed to the accepted descriptions of the lesion of Kaposi's disease.<sup>1, 2, 3, 4</sup> A point of interest in this instance in addition to the lack of skin lesions is that the brain and thyroid contained foci of the tumor. It has been stated<sup>4</sup> that no case of Kaposi's disease has been reported to have had involvement of these organs and we have been unable to find such a description. There was also cardiac involvement with the formation of an auricular thrombus. Involvement of the heart has been reported in eight cases of Kaposi's disease.<sup>4, 5</sup>

#### CASE REPORT

The patient was a 59 year old white American born tool-maker whose parents also had been born in this country. He was admitted to the hospital because of weakness of the left arm and leg of two and one half weeks' duration. The family history was irrelevant. The patient's past history is significant in that he had been admitted to the hospital one year previously because of left upper lobe lobar pneumonia due to pneumococcus type III, which responded well to sulfadiazine. He was also digitalized because of slight cardiac enlargement, auricular fibrillation and evidence of some pulmonary congestion. However, at the time of his discharge one month after admission, roentgenographic examination of the chest still showed consolidation of the left upper lobe as well as a coarse mottling throughout the entire right lung field which earlier had presented the appearance of passive congestion but which now had assumed a more nodular appearance. He was advised to return for complete re-examination after a period of convalescence but this he failed to do. From that time until his terminal illness he felt perfectly well, continued at his work, and he presented no referable complaint including respiratory distress, chest pain, cough, hemoptysis, sputum, and there was no weakness or loss of weight. Upon returning home from work two and one half weeks before his next and last hospital admission he had suddenly been seized by uncontrollable spasmodic flexion movements of his left arm and leg. There was no aura, he did not lose consciousness, nor was there urinary or fecal incontinence. He had never experienced such an episode previously. The jerking movements of the extremities subsided in about 15 minutes, but he then discovered marked weakness of these members which persisted so that he had been unable to return to his work. Five days before coming to the hospital, while walking, his left foot had caught beneath a rug, causing him to fall to the floor striking his head and left lower back. A small laceration was produced over the occiput and left him with persistent severe pain about the left sacroiliac region which caused him to come to the hospital. For approximately a year, about once a month he had been experiencing biparietal headaches each of which lasted only for a few hours and which had not been of sufficient severity to cause him to seek medical attention.

Physical examination revealed a well-nourished and well-developed man who did not appear to be chronically ill nor in any acute distress. He was completely conscious, cooperative and well-oriented. Rectal temperature was 100° F, the pulse rate was 105, respirations 22. The systolic blood pressure was 140 mm of mercury and the diastolic 90 mm of mercury. There was no pallor or cyanosis. The skin was not pigmented nor did it present the appearance of any unusual lesions. The pupils were round, regular and reacted normally to light and to accommodation. The ocular fundi showed only evidence of moderate arteriosclerotic changes. The brachial and

radial arteries were somewhat thickened but were not tortuous. Pulsations were present in the vessels of the lower extremities. The heart was moderately enlarged to the left, the apex being in the fifth interspace 10 cm left of the midsternal line. The cardiac rhythm was totally irregular, and there was a pulse deficit of 20. A soft systolic murmur was audible over the lower sternum. The lung fields were resonant throughout, vocal and tactile fremitus were within normal limits, the breath sounds were everywhere vesicular in nature, and medium moist crackling râles as well as an occasional sibilant râle were heard over both lung fields posteriorly. The abdomen was soft, there was no tenderness and no mass. Enlarged organs could not be palpated. Rectal examination was negative apart from a moderately and symmetrically enlarged prostate of normal consistency. There was no unusual adenopathy. The thyroid was of normal size, shape and consistency. The genitalia were normal and there was no palpable mass in or about the testicles. There was moderate weakness of the left hand and arm but marked weakness of the left leg. All of the deep reflexes of the left upper and lower extremities were increased although there was no clonus. The left Babinski test was positive, the Sheldon and Hoffman tests were negative. There was no sensory disturbance and vibratory and position sense remained intact. The left abdominal reflexes were diminished and the left cremasteric reflex was absent. The cranial nerves were intact.

*Laboratory Data* The red blood cells numbered 4.89 million, the hemoglobin was 14 grams per 100 cc of blood. The white blood cell count, differential count and blood smear were not unusual. The urine contained no albumin, sugar, acetone or cells, and the specific gravity was 1.024. Routine flocculation tests for syphilis were negative. The stool examinations were negative for occult blood. Lumbar puncture was performed. The initial pressure was 100 mm of water, the final pressure 80 mm of water after removal of 8 cc of fluid, the dynamics were normal. The cerebrospinal fluid was clear, contained 3 lymphocytes and 12 fresh red blood cells. The Pandy test was 3+, protein content of initial fluid was 70 mg per 100 cc and of the final fluid was 68.3 mg per 100 cc. Electroencephalography revealed abnormalities which were most marked over the right central area. The Ascheim-Zondek test was negative.

Roentgenographic examination of the skull, the sacroiliac region, flat plate of the abdomen, and intravenous pyelography revealed no abnormalities. Examination of the chest, including laminography and Bucky films, revealed numerous nodules throughout both lung fields which were characterized by radiopacity and which were rounded in appearance with indistinct borders. The interpretation was carcinomatosis of both lungs but whether this was primary carcinoma of the lungs or metastatic from without could not be ascertained from an examination of the films. The patient's general condition did not warrant a gastrointestinal series.

The day following his hospital admission, while being examined, there was noticed the sudden onset of jerking twitching movements of the muscles over the left upper abdomen at a rate of 30-40 per minute, which lasted about one and one-half minutes. On the thirteenth day he seemed somewhat clouded mentally and although he remained well-oriented his behavior seemed peculiar. On one occasion he vomited a small amount of fresh blood. Despite supportive measures his general condition became progressively worse. On the nineteenth day he lapsed into deep coma from which he never could be aroused, and he died on the twenty-fifth day. The clinical impressions were arteriosclerotic cardiovascular disease, auricular fibrillation, compensated, pulmonary carcinomatosis, primary site not established, the nature of the central nervous system lesion remained obscure but might be attributed to metastatic cerebral neoplasm, cerebral embolus from an auricular mural thrombus or possibly cerebral thrombosis.

*Necropsy* The body was that of a well-developed and fairly well-nourished



## PLATE 1

- FIG 1 Hemorrhagic tumor masses in brain  
 FIG 2 Photomicrograph of spindle-shaped tumor cells H & E stain,  $\times 150$   
 FIG 3 Hemorrhagic mass in wall of jejunum  
 FIG 4 Thrombus in left auricle  
 FIG 5 Photomicrograph of blood sinuses in tumor H & E stain,  $\times 500$

white male. It was 180 cm in length and weighed 140 pounds. A shallow decubitus ulcer was present on the left hip. The skin contained no nodules, warts, or areas of pigmentation. Two small, firm, round hemorrhagic nodules were present in the greater omentum, these were composed of a central mass of gray-white tissue surrounded by a zone of hemorrhage. A similar mass was found in the wall of the jejunum (figure 3). A healed aortic and mitral valvulitis with stenosis of the mitral valve was present in the heart. The left auricle was almost completely filled with a huge thrombus which extended into the left pulmonary vein (figure 4). No macroscopic tumor foci were discovered in the heart. All lobes of the lungs were studded with variable-sized, firm, round nodules of gray-white tumor tissue, these nodules were surrounded by narrow zones of hemorrhage and had a granulomatous appearance. One hilar lymph node was likewise involved. Similar macroscopic foci of the tumor were present in the wall of the stomach (with ulceration of the mucosa), liver, spleen, kidneys, thoracic and lumbar vertebrae, and brain (figure 1). The lesions were particularly numerous in the cerebrum, where both hemispheres and their motor areas contained multiple nodules. The brain stem and cerebellum were not involved. Two guinea pigs were inoculated with fresh tumor tissue. One was sacrificed at 79 days and was found free of lesions. The second animal was alive at 131 days without evidence of disease.

Microscopically the tumor masses varied in appearance. The overall picture was that of a granulomatous hemorrhagic sarcoma with a pleomorphic spindle cell as the dominant structural unit (figure 2). In the vertebral bone marrow the spindle cells were more differentiated than elsewhere and had a whorled arrangement. Formation of blood channels and sinusoids was particularly prominent (figure 5). In some places the blood channel walls appeared to be formed by the spindle cells whereas in other areas they were lined by endothelium. Extensive areas of hemorrhage were present in all lesions. The combination of the spindle cells with the numerous blood channels created a granulomatous appearance in many fields. Areas of necrosis with polymorphonuclear leukocytic infiltration were common. There were two accumulations of atypical cells with round or oval hyperchromatic nuclei in the left auricular thrombus. The thyroid contained a small zone occupied by pleomorphic tumor cells.

### SUMMARY

A case of Kaposi's disease (disseminated visceral idiopathic hemorrhagic sarcoma) has been presented including the clinical picture as well as the necropsy findings. This case is of particular interest because of involvement of the thyroid gland and of the brain, to our knowledge there is no recorded instance of involvement of these structures. Disseminated visceral lesions as presented by this case, in the absence of dermal manifestations, are extremely unusual.

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# SYPHILITIC HEART DISEASE PROBABLY DUE TO CON- GENITAL SYPHILIS, REPORT OF TWO CASES \*

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It is very difficult to establish the diagnosis of syphilitic aortitis in children and adolescents, and confirmation by pathological study is absolute only if the *Treponema pallidum* is found in the aorta. Stolkind<sup>1</sup> emphasized that the *Treponema pallidum* is not found in the aorta of children with congenital syphilis who are more than one year old, and for this reason the diagnosis of congenital syphilitic aortitis has rarely been proved in older children or adolescents. McDonald<sup>2</sup> has indicated that the aortic lesions of congenital syphilis differ in no way from those of the acquired form.

The order of frequency with which McCord<sup>3</sup> found the spirochete in various organs in 243 fetal autopsies is as follows: lungs, kidneys, liver, spleen, adrenals, thymus, heart, spinal cord, and aorta. At times all the organs mentioned harbored the organism, at times only one or two organs. However, he felt that if the *Treponema pallidum* were found in one organ it could be found in all.

Yampolsky and Powel<sup>4</sup> were of the opinion that aortic lesions heal rapidly when antisyphilitic therapy is instituted early in life, and that the stigmata of early syphilitic infection are rarely seen in later life.

Cole<sup>5</sup> has reported that the average duration of life in vigorously treated cases of established syphilitic aortitis in adults is 85 months, whereas in the untreated group it is 34 months. Antisyphilitic therapy has, therefore, an allaying effect on the aortic and other lesions of acquired syphilis, but does not entirely heal the aortic lesions existing before the onset of treatment.

Morhardt<sup>6</sup> has discussed several interesting aspects of the pathogenesis of syphilitic aortitis. He has written that superinfection rarely occurs in syphilis but that the tertiary stage of acquired syphilis is the period in which it is most likely to occur, that is, 15 to 20 years after the primary infection. Therefore, it would seem reasonable that a congenital syphilitic after the age of puberty may be susceptible to the *Treponema pallidum* and that superinfection may be responsible for any discoverable syphilitic lesions. Also, a state of syphilitic allergy may exist in the descendants of infected parents, and this syphilitic allergy may be responsible for an accelerated type of infection, may shorten the period elapsing before the appearance of aortic lesions, and may cause a rapid and progressive aggravation of already existing aortic lesions.

Eleven cases of syphilitic aortitis occurring at autopsy in patients under the age of 30 years were reported by McDonald<sup>2</sup>. There was clinical evidence of aortic valvular disease in two of them. Evidence of congenital syphilis was definitely present in two cases, in neither of which was there aortic valvular disease. There was some degree of narrowing of the coronary ostia in all.

Yampolsky and Powel<sup>4</sup> have described a case which seems to fulfill the requirements for a diagnosis of syphilitic aortitis of congenital origin, a nine year old colored girl whose cord blood and whose mother's blood gave positive

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Wassermann reactions There were no signs of lesions of the external genitalia to indicate acquired syphilis At necropsy syphilitic aortitis, great widening of the commissures between the aortic cusps, and extremely narrowed coronary artery ostia were found

Norris<sup>7</sup> reported two cases of sudden death due to probable congenital syphilitic aortitis The first was a nine year old girl with a positive Wassermann reaction whose family history indicated that her mother had had two stillbirths, and seven children who had died in early infancy The father had a right hemiplegia At autopsy the heart weighed 250 grams, the aortic cusps were separated, and the sinuses of Valsalva and the ascending aorta showed a thickened wrinkled intima The ascending aorta was dilated and the orifices of both coronary arteries were narrowed but not occluded Microscopic examination showed irregular intimal thickening, perivascular round cell infiltration in the media with elastic and muscle fibers broken at these points The adventitia was thick and scarred with scattered perivascular round cell formation Levaditi stain failed to demonstrate spirochetes in the aorta, myocardium, lungs, spleen, liver or kidney The second case was a 17 year old male who collapsed while pulling a cartload of wood and died a few minutes later Necropsy showed left ventricular enlargement, a heart weight of 340 grams, and thickened aortic cusps with rolled margins and thickened points of attachment The orifice of the right coronary artery was completely occluded by scar tissue extending out of the sinus of Valsalva The left coronary artery was patent but narrowed by a similar process Microscopic examination of the root of the aorta and sinuses of Valsalva showed a thickened intima with areas of mononuclear infiltration, areas of rarefaction, and round cell infiltration in the media The adventitia was thickened with numerous areas of perivascular round cell formation The aortic valves were fibrous and round cell infiltration was seen where the free edge fused with the aorta Levaditi stain of the aorta showed no spirochetes

Norris admitted that there was no conclusive evidence that the disease in either case was due to congenital syphilis No maternal Wassermann reactions were done, although the stillbirths in the first case suggested syphilis in the mother Neither patient had other lesions of congenital syphilis, and the Wassermann reactions were not obtained at an early age He also mentioned the possibility that the infection may have been acquired extragenitally after birth The age of these two patients does not preclude the possibility that the syphilitic aortitis was acquired, for although the highest incidence of clinical manifestations referable to the aorta occurs 15 to 20 years after the primary infection the interval may range from several months to 50 years

Nieman and Marks<sup>8</sup> presented the case of an 11 year old girl with productive aortitis and multiple thoracic aneurysms Pathologic examination revealed the syphilitic nature of the disease The aorta showed degeneration of the media with secondary fibrosis, fibrotic intimal thickening, proliferation of the vasa vasorum with surrounding inflammatory infiltration, and diffuse sclerosing inflammation of the adventitia These authors mentioned the possible rheumatic etiology of the aneurysms but were of the opinion that it could be excluded

To our knowledge the following patients represent the first published case reports of congenital syphilitic aortitis with valvulitis and congestive heart failure occurring in siblings The record of Case 2, a sister two years older than Case



1, came to our attention during our investigation of Case 1. She was not personally observed by us.

#### CASE REPORTS

*Case 1* S. C., a Negro girl, was seen at the age of five and one-half years at Children's Hospital, Washington, D. C., because of acute pyelitis.

The heart was recorded as normal. The liver and spleen were palpable. The blood Wassermann reaction on two occasions during this hospital stay was strongly positive. Spinal fluid examination, including the Wassermann test, was negative. Antisyphilitic therapy was instituted, and table 1 is a summary of the specific treatment carried out.

TABLE I

Time Interval	Antisyphilitic Treatment	Blood Test	Weight	Comment
March 1924 to January 1925	17 injections of 0.285 gm. of neoarsphenamine	Wassermann 4 plus	42 to 48 pounds	Ophthalmologist wrote, "Luetic disease with hemorrhage into right eye."
1925	27 injections of 0.285 gm. of neoarsphenamine			
1926	28 injections of 0.3 to 0.36 gm. of neoarsphenamine			
1927	17 injections of 0.3 to 0.36 gm. of neoarsphenamine 14 injections of bismarsen, $\frac{1}{4}$ ampule	April 1927 Wass 3 plus Kahn 4 plus  Nov 1927 Wass negative  Jan 1928 Wass negative		

She was admitted to Gallinger Municipal Hospital for the first time in December 1938. The hospital chart for this admission has been lost. However, the discharge diagnosis was syphilitic heart disease, acute salpingitis, and blindness.

She was readmitted to the Gynecological Department of Gallinger Hospital in October 1939 because of bilateral salpingo-oophoritis. On this occasion the notation was made that she had been blind since the age of 11. She had given birth to a normal child in 1936. The significant findings other than those related to her pelvic difficulties were as follows: Blood pressure 125 mm. Hg systolic and 50 mm. diastolic, bilateral keratitis, heart enlarged downward and to the left with the maximal apex impulse in the sixth interspace 10 cm. from the midsternal line. A loud systolic murmur was heard at the cardiac apex and in the aortic area to the right of the sternum. There was a loud diastolic murmur along the left sternal border. Scoliosis of the lower thoracic and upper lumbar vertebrae was described also. The Kahn reaction of the blood was negative.

In October 1940 she was admitted to the Medical Service for evaluation of her cardiac status. This was the first time she was seen by us. Physical examination showed marked systolic pulsation of the arteries of the neck and extremities, and nodding of the head with each contraction of the heart. There was frontal bossing and prominence of the ends of all the long bones. The corneae of both eyes were opaque. Her nose was flattened with a moderate amount of saddling. There were supernumerary cusps of the molar teeth. The cardiac apex impulse was diffuse, with

the point of maximal intensity in the sixth interspace 10.5 cm from the midsternal line. A loud blowing diastolic murmur was heard along the left sternal border and in the aortic area to the right of the sternum, accompanied by an intense thrill. At the apex a long low-pitched diastolic rumble ending in a slight crescendo was heard. The first sound at the apex was not unusually loud or snapping. The breath sounds were normal. A teleroentgenogram showed a large heart with particular prominence of the left ventricle and what was either an aneurysm or marked dilatation of the ascending aorta (figure 1). Fluoroscopic examination showed a much widened and vigorously pulsating ascending aorta without aneurysm. The arch and descending thoracic aorta seemed normal. Kahn reactions of the blood and spinal fluid were negative.



Fig 1 Teleroentgenogram of Case 1, showing a large heart, with particular prominence of the left ventricle and marked dilatation of the ascending aorta

In the period from October 1940 to August 1941 there were five admissions to the hospital because of increasing shortness of breath on exertion, leading to considerable dyspnea at rest, and progressively severe substernal pain, radiating down the left arm, related at first to effort and later occurring at rest. Physical examination did not reveal any new findings. The blood pressure was consistently 120 to 130 mm Hg systolic, and 30 to 40 diastolic in both arms. She was digitalized in October 1940.

On August 10, 1941 she entered the hospital because of nausea and vomiting, dyspnea, and substernal pain on slight effort. The nausea and vomiting were decreased when digitalis was omitted temporarily. On the eighth hospital day she suddenly became very dyspneic and cyanotic. There were frequent premature beats and numerous rales at the bases of both lungs. She died four hours after the onset of the acute distress. Her age at death was 22 years.

Postmortem examination showed a well developed young colored woman of slight body build, with whitish opaque corneae. The pericardial cavity contained

250 c c of serosanguinous fluid. The heart was very large, weighing 900 grams. The left ventricle was dilated and its walls especially hypertrophied. Its greatest thickness measured 18 mm. The right ventricle was 5 mm thick. There was a moderate amount of dilatation of the mitral ring, but all valves except for the aortic were normal. There was marked dilatation of the ascending aorta and aortic ring. The commissures were but slightly widened. The aortic cusps in their central part were moderately rolled and thickened. The orifice of the right coronary artery was slightly narrowed and that of the left coronary artery was decreased by at least 50 per cent owing to thickening of the intima. The wall of the aorta was greatly thickened throughout, measuring 3 mm. There was no tree barking or characteristic syphilitic scarring. The remainder of the gross examination was negative except for a mild degree of passive hyperemia of the lungs and liver.

The heart was sent to Dr. Benjamin Castleman of the Department of Pathology of the Massachusetts General Hospital. He wrote as follows: "Grossly, I was unable to make any diagnosis except marked dilatation of the ascending aorta. The intima seemed to me to be very smooth, and not to show any tree barking or scars. It is true, however, that the aortic cusps were rolled and thickened, and in one place there was slight separation of the cusps at the commissure.

"I took a section through this commissure, as well as a few other sections of the ascending aorta. In our ordinary hematoxylin-eosin stain, there is no doubt of a slight but definite lymphocytic and plasma cell infiltration around the vasa vasorum of the adventitia. I could not be sure of any in the media. Elastic tissue stains, however, of the media show a very severe degeneration of the elastica (figure 2). In the usual case of syphilitic aortitis, this degeneration is ordinarily accompanied by cellular infiltration. There is no evidence of that here. However, it is conceivable that the process is so old, namely congenital, that all evidence is now gone. I would have to agree, therefore, that the best diagnosis is syphilitic aortitis, probably congenital."

*Case 2* B. C., a 12 year old Negro female, was admitted to Gallinger Municipal Hospital on March 28, 1929 with the complaint of dyspnea. She died April 9, 1929. It was learned that she had been treated at Children's Hospital, and review of her record there gave the following information. She was a full term baby. She was said to have been "purple" at birth, and bled from the nose for four days. When she was two and one-half weeks old she was admitted to Children's Hospital because of chafing of her buttocks. Examination showed peeling of the soles and palms, and excoriation of both buttocks. The liver and spleen were readily felt. The weight of the child was 7¼ pounds. The diagnosis was congenital syphilis. There is no record of a blood Wassermann at that time. Seven years later she was seen in the Out-Patient Department of Children's Hospital. The blood Wassermann was strongly positive. Antisyphilitic therapy was begun on June 14, 1924. A summary of the treatment is shown in table 2.

She was admitted to the ward of Children's Hospital on August 23, 1924 because she was not doing well. There was some disagreement concerning the exact nature of a heart murmur (or murmurs) although all examiners agreed there was a loud important murmur (or murmurs) present. Roentgen-ray of the chest on August 25, 1924 showed "hypertrophy of the left side of the heart."

Physical examination on admission to Gallinger Municipal Hospital in March 1928 revealed a markedly dyspneic and cyanotic Negro girl. Both corneae were scarred and opaque. Her extremities were cold and her body was covered with profuse perspiration. There were marked systolic pulsations of the carotid vessels. The upper incisors were peg-shaped but not notched. The cervical veins were distended and there were distinct pulsations in the suprasternal notch with a questionable pulsating tumor mass in this location. There was noted a marked precordial bulge and



FIG 2 Histological section from aorta of Case 1 magnified approximately 600 times Verhoeff's elastic tissue stain. The marked destruction of elastic tissue is shown by the large number of irregular pale areas.

diffuse cardiac impulse. The apical impulse was most intense at the left anterior axillary line. A systolic murmur was heard at the cardiac apex, transmitted to the left and also heard posteriorly. A presystolic apical murmur was also heard by

TABLE II

Time Interval	Antisymphilitic Treatment	Blood Test	Weight	Comment
June to December 1924	1 i v injection 0.125 gm and 15 i v injections of 0.33 gm neoarsphenamine	Wassermann 4 plus	48 pounds	Discharged from Antiluetic Clinic March 16, 1928
1925	23 injections of 33 gm neoarsphenamine	June 1925 Wass 4 plus  Oct 1925 Wass 1 plus		
1928	31 injections of 34 gm neoarsphenamine	Nov 1926 Wass negative		
July 1927 to January 1928	15 injections of $\frac{1}{4}$ ampule bismarsen	Jan 1928 Wass negative  June 1928 Wass negative		

some examiners. In the aortic area along the right sternal border a diastolic murmur was heard. The pulmonary second sound was accentuated. There was dullness at both lung bases with moist râles in the same area. The abdomen was distended and tympanitic with the liver edge one to two fingers' breadth below the costal margin. There was no edema noted. The temperature was 94.6° F, pulse 100, respirations 60, blood pressure 140 mm Hg systolic and 90 mm diastolic. The red cell count was 3,900,000 with 62 per cent hemoglobin, the white cell count was 20,000 with 80 per cent polymorphonuclears, 2 per cent young forms, and 18 per cent lymphocytes. The specific gravity of the urine was 1.022, and there was a large amount of albumin present as well as numerous hyaline casts. The non-protein nitrogen was 64.2 mg, creatinine 17 mg. The blood Kahn reaction was negative.

She was digitalized and given sedatives and glucose intravenously. Her condition improved during the following six days except for the development of pitting edema of the lower extremities and signs of digitalis intoxication. Electrocardiogram on April 3, 1929 showed sinus tachycardia, rate 115, P-R interval 0.2 second, upright T-waves in Leads I and II, diphasic T-waves in Lead III, and slight sagging of the S-T segments in Leads II and III.

After the first week in the hospital, she grew steadily worse. There was increasing dyspnea and cyanosis. The temperature was usually subnormal, but occasionally it rose to 100.5° F. She died on the twenty-first hospital day.

Postmortem examination showed marked enlargement of the heart, particularly to the left. The pericardium was normal. When the heart was opened, all chambers were found to be dilated, particularly those of the left ventricle and left auricle. The wall of the left ventricle was markedly thickened, measuring 17 mm. There was marked sagging of the commissures of the aortic valve and the leaflets were curled. The aorta was moderately dilated above the valves and there were diffuse linear striations through the thoracic aorta. There was a small amount of free fluid in each pleural cavity. Both lungs were moderately congested and edematous. The left lung was slightly compressed by the enlarged heart. The liver was found to extend three fingers' breadth below the costal margin. On section it was found to be firm and smooth. The brain was described as appearing normal on cut section. The pathological diagnosis was syphilitic heart disease. Unfortunately, histologic sections from this case are not available, nor is there an adequate description of them.

## DISCUSSION

Wassermann or Kahn tests of the mother's blood or of the umbilical cord blood were not made in either of these cases, and it is possible that extragenital syphilis may have been acquired in either or both between the time of birth and the discovery of their positive reactions. However, the diagnosis of congenital syphilis in the first patient seems to be reasonably certain on the basis of the positive Wassermann reaction at the age of five years and the development of interstitial keratitis even though she was receiving antisyphilitic treatment. It does not seem possible to explain the clinical picture noted first three years before her death, of angina pectoris, dilatation of the ascending aorta, free aortic regurgitation (the rumbling diastolic murmur at the cardiac apex undoubtedly represented an Austin Flint murmur), and the pathologic findings by any other process than syphilitic aortitis. The occurrence of late cardiovascular syphilis despite reasonably good (though inadequate by present day standards) antisyphilitic treatment is unusual, but possible. The Cooperative Clinic Group has reported<sup>10</sup> that despite adequate syphilitic treatment about 10 per cent of patients who were at least two years of age at the start of treatment showed relapse or progression of the disease.

The other patient reported here presents a similar picture and most of the above statements apply to this case also. The skin and mucous membrane changes frequently seen in congenital syphilis were observed when she was two and one-half weeks of age, although the blood Wassermann reaction was not recorded until seven years later. The appearance of interstitial keratitis is further evidence of congenital syphilis. In this patient antisyphilitic treatment was scattered over a period of three and one-half years, and the difference in the treatment of the two patients may account, at least in part, for the earlier development of syphilitic aortitis and its more rapid course in the second patient.

Although the *Treponema pallidum* was not demonstrated in either case at postmortem examination and good sections for histological study were not available from the second case, the pathological findings seem sufficiently characteristic to warrant a diagnosis of syphilitic heart disease. It does not seem possible to explain the histologic findings from the sections of the aorta of the first patient otherwise than on the basis of syphilis.

## SUMMARY

The occurrence, despite specific treatment, of syphilitic heart disease in sisters aged 22 and 12 years at the time of death is reported. It is probable that the heart disease in both patients was due to congenital syphilis.

We are grateful to Dr. Harold V. Connerty, pathologist at Gallinger Hospital, for his help.

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## EDITORIAL

### *ETIOLOGY AND TREATMENT OF CIRRHOSIS*

UP until the last decade portal cirrhosis of the liver was generally regarded as a hopeless disease which must sooner or later terminate fatally in spite of all therapeutic efforts. While granting that the etiology of the disorder was poorly understood, many were content, on the basis of purely circumstantial evidence, to point an incriminating finger at alcohol as the chief offender. Although there can be no question that alcoholism is the most common antecedent factor in victims of cirrhosis in this country, Patek<sup>1</sup> found that in 30 per cent of cirrhotic patients seen at autopsy no history of alcoholism was obtained. He suggested that the etiologic rôle of alcoholism is an indirect rather than a direct one and that alcohol per se does not cause cirrhosis of the liver. The fact that the disease occurs commonly in India, Java, and Ceylon, where alcoholism is rare, would support such an interpretation. Moreover, cirrhosis is known to follow severe toxic hepatitis, as for example from carbon tetrachloride or certain arsenical drugs, and so-called infective or epidemic hepatitis in non-alcoholic individuals. Since alcoholic beri-beri and pellagra have been shown to be similar to the endemic forms of these diseases, it seemed plausible to Patek that the correlation between alcoholism and cirrhosis might likewise be due to a coexisting nutritional deficiency. The heavy drinker will frequently subsist on alcohol alone for long periods with little or no food, thus it would seem reasonable to assume that many of the morbid states to which the alcoholic is peculiarly subject are primarily manifestations of nutritional deficiency. Alcohol may conceivably exert toxic effects in the face of a poor diet, but it must play a minor rôle at best, since all of the deficiency syndromes may develop in total abstainers on deficient diets.

In the experimental field an abundance of evidence has accumulated over the past twenty years attesting to the etiologic rôle of nutritional deficiency in the production of liver disease. Allan<sup>2</sup> and his associates in 1924 reported that depancreatized dogs receiving adequate amounts of insulin and a diet of lean meat, sucrose, and bone ash did not survive for longer than a few months. They further observed that failure of liver function due to fatty infiltration of the liver found in such animals could be prevented by adding raw pancreas to the diet. These observations deserve special recognition in that they provided the essential stimulus to extensive research in

<sup>1</sup> (a) PATEK, A. J., and POST, J. Treatment of cirrhosis of the liver by nutritious supplements rich in vitamin B complex, *Jr Clin Invest*, 1941, xx, 481. (b) PATEK, A. J. Dietary treatment of Laennec's cirrhosis with special reference to early stages of the disease, *Bull New York Acad Med*, 1943, xix, 498.

<sup>2</sup> ALLAN, F. N., BOWIE, D. J., MACLEOD, J. J. R., and ROBINSON, W. L. Behavior of depancreatized dogs kept alive with insulin, *Brit Jr Exper Path*, 1924, v, 75.



widely scattered laboratories on lipotropic substances, or substances preventing the deposition of fat in the liver, among them lecithin, "lipocair," choline, methionine, and inositol. This experimental work may be briefly summarized as follows. Fatty livers and eventually cirrhosis have been produced in normal dogs, rats, and rabbits, maintained on diets high in fat and low in protein or certain highly purified diets. These liver changes may be prevented by increasing the intake of protein (particularly casein), by the addition of yeast or such lipotropic substances as have been enumerated. Although certain discrepancies crop up in the reported results, depending upon the composition of the diet and the type of experimental animal used, yet the evidence is most convincing that crude sources of vitamin B complex and such relatively simple chemical substances as choline and methionine exert a remarkable protective action upon the liver. It has further been found that the addition of cystine to certain of the diets may aggravate the hepatic lesions. The whole problem of cystine-methionine-choline offers a fascinating field for future research.

Undoubtedly, clinical and experimental observations have been equally important in giving impetus to the development of the current treatment of human cirrhosis by a nutritious diet high in calories, protein, and vitamins. Early in this century diets low in all constituents were usually prescribed for cirrhotic patients in order to "spare" the diseased liver as far as possible. In the 1920's, as a result of animal experiments showing the value of a high carbohydrate intake in protecting the liver against certain poisons, diets high in carbohydrate (but still relatively low in protein) were introduced into the therapy of cirrhosis in human beings. Saline purges and diuretics were freely employed, while surgical procedures were devised to improve collateral circulation in the hope of relieving ascites. It was not until 1937 that Patek first reported promising results from the treatment of cirrhosis with a high-caloric diet, rich in protein as well as carbohydrate and fat, and supplemented with large amounts of brewer's yeast powder, vitamins, and injections of liver extract. This contribution marks the beginning of a new era in the therapy of cirrhosis. Convinced that the improvement that followed treatment was beyond chance expectations, Patek was encouraged to extend his therapeutic project to embrace a larger series of patients over a longer period of time. By comparing the results of such treatment in 54 patients suffering from decompensated cirrhosis with a control series of 386 "untreated" patients, he was able to present statistically supported evidence of the efficacy of his therapeutic regimen. Of the treated group 60 per cent experienced spontaneous disappearance of ascites in contrast to only 7 per cent of the control group. The survival rate for patients two years after the onset of ascites was 45 per cent for the treated group as against 22 per cent for the "untreated." Patek predicts with good reason that far superior results might be expected if the dietary treatment could be instituted earlier in the disease before signs of hepatic decompensation had appeared.

Fleming and Snell<sup>3</sup> have obtained similar results in the treatment of 50 cirrhotic patients with a diet that differed materially from Patek's diet in that it was higher in carbohydrate, low in fat, and high in protein not derived from meat sources, whereas Patek gave large servings of meat and as much as 175 grams of fat daily. The basis for this change in protein composition was Bollman's observation that animals with hepatic injury are made worse by administration of meat or meat extracts while tolerating protein from other sources without harmful effect. Snell also supplemented his diet with various pure vitamins, crude oral liver extract, and yeast or yeast concentrates. Subsequently, Keefer and Fries<sup>4</sup> have stressed the therapeutic value of a high carbohydrate, low fat diet with a moderate protein content, supplemented with vitamin preparations and liver extract, in a series of 70 alcoholic patients with fatty livers. They regard the fatty liver as the precursor of cirrhosis, but point out that jaundice, ascites, and death may occur during the stage when the liver is filled with fat and before actual fibrosis has developed. The recognition of the disorder in its early stages and the use of appropriate treatment was followed in many cases by recovery.

In view of the volume of experimental work on the lipotropic action of choline, it was only natural that this substance should be given a cautious therapeutic trial in the treatment of cirrhosis and fatty liver in man. Russakoff and Blumberg<sup>5</sup> have only recently reported highly suggestive evidence that choline exerts a beneficial effect on the clinical course of patients with decompensated cirrhosis. Their patients were placed upon a low-fat Patek dietary regimen supplemented with 1.5 to 6.0 grams of choline chloride daily. No untoward effects from the choline were noted if it was administered orally after meals. Seven of the nine patients treated adequately with choline improved, and it was the opinion of the authors that in several instances the improvement was more rapid than might have been expected from the dietary regimen alone. In a current article<sup>6</sup> reviewing the various aspects of the modern treatment of cirrhosis the writer reports suggestive beneficial effects from the addition of choline to the Patek regimen in several cases so treated. It is as yet too early to draw definite conclusions as to the value of choline in the therapy of human cirrhosis, but certainly further trial of choline, and possibly of methionine also, is desirable in patients with cirrhosis, fatty liver, and acute hepatitis, no matter what the etiology may be.

These recent clinical observations on the dietary treatment of cirrhosis may then be briefly summarized in the following manner. The most promis-

<sup>3</sup> FLEMING, R. G., and SNELL, A. M. Portal cirrhosis with ascites: an analysis of 200 cases with special reference to prognosis and treatment, *Am. Jr. Digest Dis.*, 1942, ix, 115.

<sup>4</sup> KEEFER, C. S., and FRIES, E. D. The fatty liver—its diagnosis and clinical course, *Trans. Assoc. Am. Phys.*, 1942, lvii, 283.

<sup>5</sup> RUSSAKOFF, A. H., and BLUMBERG, H. Choline as an adjuvant to the dietary therapy of cirrhosis of the liver, *Ann. Int. Med.*, 1944, xxi, 848.

<sup>6</sup> BARKER, W. H. The modern treatment of cirrhosis of the liver, *Med. Clin. N. Am.*, March, 1945.

ing treatment of fatty liver and cirrhosis today would appear to consist in the administration of a nutritious diet high in calories, carbohydrate, protein, and vitamins, especially the vitamin B complex, but relatively low in fat. The high protein content is particularly important since it is generally agreed that the hypoproteinemia (or more accurately hypoalbuminemia) so common in patients with liver disease plays a more prominent rôle than portal obstruction in the causation of ascites. The protein should be supplied in the form of lean meat, liver, eggs, milk, and cheese. There is highly suggestive evidence that injections of crude liver extract and the oral administration of choline may prove to be valuable supplements to the dietary regimen. On such a regime almost unbelievable improvement has been observed in patients with severely decompensated cirrhosis. Earlier diagnosis and early institution of an adequate dietary program should not only arrest the progress of the disease but actually result in clinical cures in the vast majority of patients.

In addition to the dietary program, certain adjunctive therapeutic measures frequently be employed depending upon special problems arising in various patients with cirrhosis. Among these procedures are the intramuscular injection of vitamin K in patients with hemorrhagic diathesis due to hypoprothrombinemia, transfusions in patients with massive hemorrhage, careful regulation of salt and fluid intake to forestall an increase in ascites and edema on the one hand or hyponatremia with dehydration on the other, the use of diuretics and, if these fail, paracentesis for relief of intractable ascites, and the various surgical operations designed to relieve ascites and to prevent hematemesis. Of the latter, omentopexy after a brief period of popularity has been largely discarded as an almost useless procedure with a high mortality rate. Cirrhotic patients tolerate anesthesia poorly and hence are not good operative risks. Injection of varices through the esophagoscope and ligation of the coronary vein of the stomach may serve to reduce the incidence of hematemesis. Splenectomy may be followed by striking improvement in an occasional patient but is too radical a procedure to be justifiable in many instances. Operations designed to shunt blood from the portal system to the vena cava may prove to be the ultimate answer to the problem.

It must be obvious that the final word has not been said as regards an ideal treatment for cirrhosis of the liver. Nonetheless, with the advent of modern dietary therapy and the improvement in surgical technic, the victim of cirrhosis today may rightly feel far more optimistic about his prospects of survival than he could have felt 50 years ago or even 10 years ago.

## REVIEWS

*The Avitaminoses* By WALTER H EDDY, Ph D, and GILBERT DALLDORF, M D  
438 pages, 23.5 × 15.5 cm The Williams and Wilkins Company, Baltimore  
1944 Price, \$4.50

The three years which have elapsed between the second and third editions of this volume have been marked by the discovery of many new facts in the vitamin field. The authors found it necessary to revise and reset the entire volume in order to cover these many changes. They have tabulated more of their material and have regrouped related figures and formulae with the result that they have presented up to 50 per cent more material without increasing the length of the book.

The material relating to the chemical nature and function of the vitamins and that concerning the mild and extreme deficiency states have been put in sections one and two of the volume, respectively. The third section includes a new chapter on vitamin assay methods and one on laboratory tests useful in the diagnosis and study of the vitamin deficiency states. The chapters on the chemical nature of the vitamins and on cellular oxidation have been rewritten and the relationship between certain vitamins and oxidation reduction systems has been stressed. In addition to the members of the B complex discussed in the previous edition, inositol, para amino benzoic acid, biotin, choline, and folic acid are included in the chemical characterization of members of the B complex. This brings to 15 the vitamins listed in the volume as proved by chemical means to exist.

The chapter on vitamin requirements is now based primarily upon the recommendations of the Food and Nutrition Board of the National Research Council. The U S Food and Drug Standards for label control are also cited.

"The Avitaminoses" should continue to be a valuable reference volume for anyone interested in the vitamin field.

M A A

## BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Anatomy as Basis for Medical and Dental Practice* By DONALD MAINLAND, M B, Ch B, D Sc, F R S E, F R S C 863 pages, 24 × 16.5 cm 1945 Paul B Hoeber, Inc, New York Price, \$7.50

*Approved Laboratory Technique* Fourth Edition By JOHN A KOLMER, M S, M D, Dr P H, Sc D, LL D, L H D, F A C P, and FRED BOERNER, V M D 1017 pages, 25 × 17 cm 1945 D Appleton-Century Company, New York Price, \$10.00

*Recent Advances in Endocrinology* Fifth Edition By A T CAMERON, M A, D Sc, F R I C, F R S C 415 pages, 14 × 20 cm 1945 The Blakiston Company, Philadelphia Price, \$5.00

*The Marijuana Problem in the City of New York* By the Mayor's Committee on Marijuana 220 pages, 23.5 × 15.5 cm 1944 The Jaques Cattell Press, Lancaster, Pennsylvania Price, \$2.50

*The Abortion Problem* Proceedings of the Conference Held under the Auspices of the National Committee on Maternal Health, Inc, at the New York Academy of Medicine, June 19 and 20, 1942 HOWARD C TAYLOR, JR, M D, Conference

- Chauiman 182 pages, 23.5 × 15.5 cm 1944 The Williams and Wilkins Company, Baltimore
- Essentials of Allergy* By LEO H. CRIEP, M.D., with a foreword by ROBERT A. COOKE, M.D. 381 pages, 20 × 13 cm 1945 J. B. Lippincott Company, Philadelphia Price, \$5.00
- Casualty Work for Advanced First-Aid Students* By A. W. MACQUARRIE, M.B., Ch.B. (Edin.) 231 pages, 12.5 × 9.5 cm 1944 E. & S. Livingstone Ltd, Edinburgh (Imported by the Peter Reilly Co., Philadelphia) Price, \$1.80
- Arterial Injuries Early Diagnosis and Treatment* By The Vascular Injuries Subcommittee of the M.R.C. War Wounds Committee Medical Research Council War Memorandum No. 13 24 pages, 24.5 × 15 cm 1944 His Majesty's Stationery Office, London Price, \$1.0
- The Treatment of "Wound Shock"* (Instructions produced by the Medical Research Council Committees on Traumatic Shock and on Blood Transfusion, in cooperation with the Army Medical Service) Medical Research Council War Memorandum No. 1—Second Edition 32 pages, 24.5 × 15 cm 1944 His Majesty's Stationery Office, London Price, \$1.5
- Internal Medicine Its Theory and Practice in Contributions by American Authors* Fourth Edition Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P. 1518 pages, 25.5 × 15.5 cm 1945 Lea & Febiger, Philadelphia Price, \$10.00
- Microbiology and Pathology* Third Edition By CHARLES F. CARTER, B.S., M.D. 777 pages, 22.5 × 14.5 cm 1945 C. V. Mosby Company, St. Louis Price, \$3.50
- Physical Demands of Daily Life An Objective Scale for Rating the Orthopedically Exceptional* By GEORGE G. DEEVER, M.D., and MARY ELEANOR BROWN, M.A. 36 pages, 23 × 15.5 cm 1945 Institute for the Crippled and Disabled, New York City Price, \$1.0
- Chronic Pulmonary Disease in South Wales Coalminers II Environmental Studies* A Report by the Committee on Industrial Pulmonary Disease B-G Reports on Physical, Chemical and Petrological Studies by T. BEDFORD and C. G. WARNER, H. V. A. BRISCOE, P. F. HOLT, N. SPOOR and others, G. NAGELSCHMIDT, A. BRAMMALL and J. G. C. LEECH, D. HICKS and G. NAGELSCHMIDT, J. IVON GRAHAM and D. F. RUNNICKLES, and coworkers (Medical Research Council) 222 pages, 24 × 15.5 cm 1943 His Majesty's Stationery Office, London Price, 10s. 6d. net

# COLLEGE NEWS NOTES

## NEW LIFE MEMBERS

Since the publication of the last issue of the ANNALS OF INTERNAL MEDICINE, the following Fellows of the College have become Life Members (listed in the order of subscription)

Dr Harold F Koppe, Dayton, Ohio  
Dr Harvey M Ewing, Montclair, N J  
Dr Homer Deeter Cassel, Dayton, Ohio  
Dr Otto A G Reinhard, Lincoln, Nebr  
Dr Charles Henry Parsons, Concord, N H  
Dr Lawton M Hartman, York, Pa  
Dr Leopold Shumacker, Chattanooga, Tenn  
Dr Anita Mary Muhl, San Diego, Calif  
Dr Donald R McKay, Buffalo, N Y  
Dr William Lindsay Miller, Gadsden, Ala  
Dr Samuel G Shepherd, Philadelphia, Pa  
Dr William D Stroud, Philadelphia, Pa

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## A C P MEMBERS IN THE ARMED FORCES

Dr Aloysius J B Connolly (Associate), Washington, D C, is a Lieutenant Commander in the U S Naval Reserve, having been on duty since 1943, but not previously recorded with the College This brings the total number of members who have entered upon military duty to 1,856

The following members of the College have been honorably discharged

Dr William W Alexander (Major, MC, AUS), Florence, Ala  
Dr Chester S Fresh (Major, MC, AUS), New Orleans, La

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## GIFTS TO THE COLLEGE LIBRARY

### *Book*

F Dennette Adams, F A C P, Colonel, (MC), AUS—"Physical Diagnosis," 13th Edition

### *Reprints*

J Edward Berk, F A C P, Captain, (MC), AUS—1 reprint  
Dr Walter L Bierring, F A C P, Des Moines, Iowa—1 reprint  
Abraham G Cohen, (Associate), Major, (MC), AUS—1 reprint  
Dr Julius H Comroe, Jr, F A C P, Philadelphia, Pa —4 reprints  
Dr C C deGravelles, F A C P, New Iberia, La —1 reprint  
Dr M V Hargett, F A C P, Hamilton, Mont—1 reprint  
Dr Jerome G Kaufman, F A C P, Newark, N J—1 reprint  
William C Meredith, F A C P, Lieutenant Commander, (MC), USNR—1 reprint  
Julius R Pearson, F A C P, Captain, (MC), AUS—1 reprint  
Dr Franklin B Peck, F A C P, Indianapolis, Ind—1 reprint  
Dr Lawrence E Putnam, (Associate), Washington, D C—2 reprints  
Dr George X Schwemlein, (Associate), Chicago, Ill —1 reprint

Dr Sidney A Slater, F A C P, Worthington, Minn—2 reprints  
 Dr Norman Strauss, F A C P, New York, N Y—1 reprint

### EXAMINATIONS BY CERTIFYING BOARDS

AMERICAN BOARD OF INTERNAL MEDICINE, William A Weriell, M D, Assistant Secretary-Treasurer, 1301 University Avenue, Madison 5, Wis

*Written Examination* Tentatively scheduled for mid-autumn, 1945, in various centers throughout the United States, also available to candidates in military and naval services at certain of their stations, with permission of their commanding officers Applications for civilian candidates should be filed by early August Every effort will be made to accommodate candidates in the Service, regardless of the closing date for the acceptance of applications

*Oral Examination* Oral examinations are tentatively planned for June 6, 7 and 8 in Philadelphia Consult the Assistant Secretary-Treasurer concerning other oral examinations

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY, George M Lewis, M D, Secretary-Treasurer, 66 East 66th Street, New York 21, N Y

*Written Examination* For B candidates, given in different cities throughout the country, April 23

*Oral Examination* For A and B candidates, New York City, June 8-9, 1945

AMERICAN BOARD OF PEDIATRICS, C A Aldrich, M D, Secretary, 115½ First Avenue, S W, Rochester, Minn

*Written Examination* Tentatively planned about October, 1945

*Oral Examination* New York City, March 29, 30 and 31, and Chicago, May 12-13, 1945 The lists for these oral examinations are reported to be filled already It is planned to have the next succeeding oral examination during November or December, 1945 Consult the Secretary

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, Walter Freeman, M D, Secretary-Treasurer, 1028 Connecticut Avenue, N W, Washington, D C

*Written Examination* At various cities throughout the country, March 30, 1945

*Oral Examination* Chicago, May 18-19, 1945

AMERICAN BOARD OF RADIOLOGY, B R Kirklin, M D, Secretary-Treasurer, Mayo Clinic, Rochester, Minn

This Board conducts only a general oral examination Exact date of next examination not yet determined, but it will be held during the late autumn, 1945 Consult the Secretary-Treasurer

AMERICAN BOARD OF PATHOLOGY, F W Hartman, M D, Secretary-Treasurer, Henry Ford Hospital, Detroit 2, Michigan

*Written Examination* Pathologic anatomy, June 13, clinical pathology, June 14, at Temple University School of Medicine, Philadelphia, Pa

### A C P MEMBERS, LOS ANGELES REGION, ADDRESSED BY DR STROUD

Under the Governorship of Dr Roy E Thomas, F A C P, members of the College of the Los Angeles region held a dinner meeting on February 23 Dr William D Stroud, Treasurer of the College, Philadelphia, was the guest speaker He outlined the work and plans of the College, and gave a paper on hypertension and capillary fragility There were about sixty Fellows and Associates present, and the meeting was acclaimed a success

LT COMDR WILLIAM M SILLIPHANT  
RESCUED FROM BILIBID HOSPITAL, MANILA

Lt Comdr William M Silliphant, (MC), U S Navy, was rescued during February from the Japanese military prison camp at Bilibid Hospital, Manila. Commander Silliphant is an Associate of the College and was reported to us as "missing in action" at the time of the fall of the Philippines. We had been unable to confirm any facts about his whereabouts until March 2, 1945, when we received a letter from him, written at the Bilibid Hospital February 1, 1945, before United States Forces had yet reached Manila. Commander Silliphant, however, knew that General MacArthur's forces were not far away, and he had absolute faith that he and other prisoners would surely be rescued soon, and so he couldn't wait but prepared his letter in advance for release immediately after rescue. He said in part, "You may not have been aware that for the past three years, I had been the unwilling guest of His Imperial Majesty of Nippon, and unfortunately had been unable to communicate with you. At the present time I am still behind the enemy lines, but the situation seems to be improving rapidly for us here. I am writing this letter at this time in order to have it ready for the first mail out after our rescuers arrive, and I hope it shall not be too long delayed."

Commander Silliphant was assigned to the U S Naval Hospital, Canacao, Philippine Islands, in November, 1941, as Laboratory Officer and Assistant in Medicine. This hospital was subsequently re-organized as the Bilibid Hospital for military prison camps of the Philippine Islands. Further details about Commander Silliphant may not yet be published, but we hope to have further data available later.

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CAPTAIN EDWARD L BORTZ IN IWO JIMA

Captain Edward L Bortz, (MC), USNR, of Philadelphia, for many years active on the College program of postgraduate courses, and the College Governor for Eastern Pennsylvania, served throughout the Iwo Jima campaign on one of the Evacuation Hospital staffs. A letter near the end of the campaign relates that our Marines have been magnificent and that there are many heroes among our Privates First Class. He relates how the Medical Officers as well as all others have been sleeping in foxholes, that living is rugged, that they were frequently bombed during the nights and that it is a bit difficult to sleep in the open with shells whistling overhead. On an island so small it is obvious that no one could be far from the front.

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TYPICAL MESSAGES FROM WAR AREAS

The College Office receives many letters from its members in all parts of the world, and acknowledges them with deep appreciation, because the College wishes to maintain its contacts with its members everywhere.

"In December, 1943, I was reassigned to the 219th General Hospital (Pacific area) and since then have been Chief of the Cardiovascular Section and for the past three months Chief of the Officers and Women's Medical Sections as well. This work has been much more pleasing to me, since it is quite in keeping with the sort of work I did in private practice. You may be interested to know that our Chief is Lt Col Conrad Acton, Life Member of the College. The chief desire of everyone who has been out here for a long time is that this war may soon be over and that we may return home. We realize that the end is not yet in sight, however, and we realize the importance of good medical care for our soldiers. This is a beautiful



place from most standpoints Our facilities are probably as good as the Army can offer anywhere, and we have no physical hardships The separation from our loved ones is the greatest hardship we have to bear"—Captain, (MC), AUS (F A C P, Detroit, Michigan)

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#### REPORT CHANGES OF ADDRESS<sup>1</sup>

The ANNALS OF INTERNAL MEDICINE and the Office of the American College of Physicians experience great difficulty in obtaining address changes for subscribers who are in the Armed Forces, and who themselves overlook recording new assignments with the College Office A great effort is made to follow each member and subscriber, but it is extremely difficult to obtain new addresses except through the individual himself Many copies of the ANNALS OF INTERNAL MEDICINE, as well as other journals, are lost because members, especially those on active military duty, fail to record their correct addresses

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#### DR NELSON G RUSSELL, F A C P, RECEIVES HONOR

The Chancellor's Medal of the University of Buffalo was conferred upon Dr Nelson G Russell, F A C P, on the occasion of the 45th annual mid-year convocation of the University on February 22

The citation started, "Nelson Gorham Russell, scientist, soldier, civic leader, teacher and mentor of two generations of physicians " Dr Russell is a graduate of the Medical School of the University of Buffalo, and he has given many years of devoted service there as Professor of Medicine (now Emeritus) The local press states that in very large part Dr Russell deserves credit for advancing the School to the high position that it now has among such institutions in the nation, that he has put his impress upon hundreds of young men whose services dignify it

During World War I he was designated Consultant in General Medicine for an area in which there were some thirty hospitals, the appointment having been made by General Pershing Dr Russell received a citation for "exceptionally meritorious and conspicuous services" He also received the Purple Heart

Dr Russell is Chairman of the Buffalo Advisory Board of Health and of the Managing Board of the Meyer Memorial Hospital

"His career has been one of constantly enlarging service He is an exemplar of the finest traditions of his profession The Chancellor's Medal was never more worthily bestowed"

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#### DR SIDNEY A SLATER HONORED

Dr Sidney A Slater, F A C P, Superintendent of the Southwestern Minnesota Sanatorium, at Worthington, Minnesota, and a recognized authority on tuberculosis and public health, will be honored by his alma mater, the Medical College of Virginia, at a special convocation on April 27, when he will receive the degree of Doctor of Science At the same time Dr Slater will receive a previously awarded Phi Beta Kappa key

DR JOSEPH T WEARN APPOINTED DEAN  
WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE

Dr Joseph T WEARN, F A C P, Professor of Medicine at Western Reserve University, has been appointed Dean of the School of Medicine. He succeeds Dr Torald H Sollmann, F A C P, who retired last July 1, after nearly 50 years of service with the University. Dr Wearn will continue as Professor of Medicine at the University, and as Director of the Department of Medicine at Lakeside Hospital. He is widely known as a teacher and for his research in medicine. He has written extensively on the physiology of heart disease, diseases of the blood, including leukemia, and other subjects. He is a Consultant to the Surgeon General of the United States Army, Consultant to Research and Development Branch of the Office of the Quartermaster General of the U S Army, Chief of the Division of Physiology, Committee of Medical Research, and Chairman of the Subcommittee on Blood Substitutes, of the Office of Scientific Research and Development.

Dr Wearn went to Western Reserve and Lakeside Hospital in 1929 from Harvard Medical School, where he was Associate Professor of Medicine and Associate Director of the Thorndike Memorial Laboratory and Visiting Physician at the Boston City Hospital.

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POSTGRADUATE COURSES OFFERED BY THE COLLEGE

The spring 1945 schedule of Courses has been published in several of the preceding issues of this Journal. The roster included five courses: Cardiology, at Columbia University College of Physicians and Surgeons, under Dr Robert Levy, F A C P, Director; Mechanics of Disease, at Harvard Medical School, under Dr George Thorn, F A C P, Director; Clinical Medicine-Hematology, at Ohio State University College of Medicine, under Dr Charles A Doan, F A C P, Director; Gastrointestinal Diseases, at the Graduate Hospital, Philadelphia, under Dr Henry Bockus, F A C P, Director; and, Applications of Psychiatry to the Practice of Internal Medicine, at the University of Wisconsin Medical School, under Dr Hans Reese, F A C P, Director.

The organization of these refresher courses has become one of the most keenly appreciated activities of the College. The demand for these courses among members of the College is greater than available facilities. During the present wartime it is difficult to find faculties that are available and prepared to give courses on the high plane set by the College. There is an admirable willingness to aid the program everywhere.

Two situations conspired during the winter, delaying the appearance of the Postgraduate Bulletin. (1) The program had to be submitted to the Office of Defense Transportation for approval, which resulted in a very considerable delay, during which time the Bulletin could not be released for printing. Finally, the ODT added its conditional approval, providing the registration in any course shall not exceed 50 men who will be using transportation and housing facilities. (2) Although the Postgraduate Bulletin was rushed to completion and sent to most parts of the country by first-class mail, with allowances being made for distances, there were numerous reports of delay or loss in the mails.

Announcements concerning the courses appeared in several issues of the ANNALS OF INTERNAL MEDICINE with the result that many members registered in advance of the arrival of the Bulletin. All courses were filled to capacity, and many applicants had to be disappointed. In some courses, such as the one in Cardiology in New York City, the faculty could have handled a much larger number, yet the regulations of the Office of Defense Transportation made this impossible, because of limitation of registration.

The program of courses for the autumn of 1945 is already being organized. Dr Paul White, of Harvard Medical School, will give a 1-week course in Cardiology, repeating the very popular course given by him during the autumn of 1944. Members are invited to write in to the College Headquarters stating the titles of courses desired, the Committee on Postgraduate Courses will make an effort to extend the program along the lines most desired by the College members.

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Dr R K Richards, F A C P, North Chicago, Illinois, addressed the Chicago Neurological Society, January 10, on "The Pharmacology of Tridione, a New Experimental Drug for the Treatment of Convulsive and Related Disorders."

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The Society of Medical Jurisprudence conducted a Symposium at the New York Academy of Medicine Building, February 19, on the subject, "Is the Obligation of Providing Medical Care to All—That of the State, the Public or the Medical Profession?" Dr Nathan B Van Etten, F A C P, spoke on the subject from "The Standpoint of the Practitioner of Medicine", Colonel Louis H Bauer, F A C P, discussed "The Standpoint of Organized Medicine", Dr William W Herrick, F A C P, President of the New York Academy of Medicine, discussed the "Federal Social Security Health Legislation", Honorable William F Bleakley, Former Justice of the New York Supreme Court, talked on "The Probable Attitude of the Public in Regard to the Future of Medicine in the United States", Allen Wardell, Esq, President of the New York City Bar Association, used as his subject, "Should the Medical Profession or the Government Provide Medical Care through Insurance?", and Mayor Fiorello H LaGuardia discussed "The Health Insurance Plan of Greater New York."

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Since March 15 the WPB has lifted the restrictions on the general distribution of penicillin for civilian use. This release, however, does not apply to the new oral penicillin in tablet form. Many of the manufacturers are developing penicillin for oral use when released by WPB, anticipated in the near future.

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#### COMMITTEE ON POSTWAR MEDICAL SERVICE

The Joint Committee on Postwar Medical Service met in Chicago on February 10 and again on March 17. The minutes of the latter meeting are not available when this copy goes to press. Dr Ernest E Irons, F A C P, is the Chairman of the Joint Committee. Due to other assignments and duties Dr Walter W Palmer, Chairman of the A C P Committee on Postwar Medical Service, recently resigned, and President Irons appointed Dr George Morris Piersol, F A C P, as Chairman of the Committee, succeeding Dr Palmer, and Dr W W Herrick, F A C P, New York City, as a member of the A C P Committee.

Among the more important transactions on February 10 was a progress report on the analysis of questionnaires sent to medical officers by Lt Col H C Lueth, F A C P, liaison officer between the Surgeon General of the Army and the Committee. His report in brief summary was as follows:

- 1 Future educational desires of medical officers on duty with the Army, Navy, Public Health Service and Veterans Administration were determined by a study of 21,029 returned questionnaires.

- 2 Nearly 60 per cent of the group, 12,534, wanted to take long courses (six months or longer) of further training in hospital or educational work. About one-

fifth of the group, 4,563, indicated they wished to take short courses (less than six months)

3 There were 3,922 medical officers, or 187 per cent of the group, who did not want any future training

4 Requests for short courses included all specialties The largest number of requests were for the following specialties in order of frequency internal medicine, surgery, general review, obstetrics and gynecology, pediatrics, otolaryngology and ophthalmology

5 The ten most popular special fields of training by means of long courses, in order of frequency of request, were surgery, internal medicine, obstetrics and gynecology, general review, psychiatry and neurology, pediatrics, orthopedic surgery, ophthalmology, radiology and otolaryngology

6 Nearly two-thirds of the group, 13,333, or 63 per cent, expressed a desire to become certified specialists There were 3,324 medical officers, nearly 16 per cent of the entire group, already certified by the American specialty boards The remainder either did not care to be certified or did not mention their desires

7 Nearly 40 per cent, 8,734 medical officers, came from private practice to the military services Twenty-two per cent, 4,640, came directly from internships, nearly 10 per cent, 2,191, came directly from residencies, and the remainder came from various types of practice About 15 per cent failed to answer the question concerning their previous type of medical practice

8 A comparison of the results of a pilot questionnaire and the present questionnaire was made Long courses were requested by about one-fifth more men in the final questionnaire than in the pilot questionnaire Only two thirds as many men requested short courses in the final questionnaire as in the pilot The difference was attributed to a change in viewpoint of medical officers during the interval between the circulation of the questionnaires rather than to an error in sampling

Dr Olin West, Secretary of the American Medical Association, reported that the Bureau of Information is now functioning and up to that time had completed tabulation of 38 states He predicted that the Bureau of Information would receive the cordial cooperation of the constituent state medical associations and the component county medical societies Inquiries coming to the Bureau are more numerous from men who have already been discharged from active service than from those still on duty The Bureau is collecting information in regard to education, licensure and location Information on educational facilities will be handled by Dr Victor Johnson, Secretary of the Council on Medical Education and Hospitals The question of location in specific communities is a local problem, which will be referred to state agencies Much confusion in the states has arisen in the selection of hospitals and educational institutions under provisions of the GI Bill, in some states the State Department of Education is advising the Governors—in several states the organization of the work is behind and in others far ahead—and it will be necessary to "tie up" the hospital, educational and licensing elements into a coordinating group The Committee on Postwar Medical Service will be able to exercise such a coordinating action

The following resolution was adopted, after discussion in which it was noted that under the GI Bill the Governors of the states are given control over all phases of education for veterans

RESOLVED, That the chair be authorized to appoint a sub-committee to

1 Draw up recommendations to the Governors of the several states concerning the medical education and postgraduate training of veterans under Title II of Public Law No 346, the Servicemen's Readjustment Act of 1944, with particular reference to the certification of institutions as qualified to give such training, and

2 Coordinate this effort with related medical and health problems in the state

Progress Report on Educational Opportunities for Medical Officers Dr Victor Johnson presented a progress report on educational opportunities for medical officers, stating that it would be necessary to modify some of the estimates of available residencies on the basis of the analysis presented by Colonel Lueth. He stated that developments so far are promising and, if institutions and individuals involved continue with the same vigor and industry, the need will be met. Further reports will be made to the Committee.

During the discussion of Dr Johnson's report, the question was asked if all of the residencies that would be available are of a type that would lead to certification by specialty boards, and the reply was that many would be second year training and that those hospitals initiating new residencies would have to be considered by the Council on Medical Education and Hospitals and by the specialty boards. This progress report will be continued at the next meeting.

Minor reports were received from the Subcommittee to Confer with the Surgeons General on Education of Medical Officers and from a Consulting Committee on Army and Navy Plans for Residencies and Graduate Study. The Army was reported to be readjusting the specialties practiced in its general hospitals, and increasing and readjusting the size of the facilities now available. The refresher professional training has been authorized for officers of the Medical Corps who for the past twelve months or longer have been in administrative command. Training will be in hospitals in both medicine and surgery, will be voluntary and available to any officer of the Medical Corps, with priority given to men who have been overseas. Such officers will be ordered to temporary duty to take the course of instruction, at their own request, and will continue in service. It was added that the refresher course plan has nothing to do with the specialties, however, and that the Army has no intention of putting these men into a type of specialized training that would qualify them for specialty board certification.

A representative of the United States Public Health Service reported that in U S Public Health Service Hospitals there will be places for about thirty residencies, available after the war. The Public Health Service is conducting a training course in civilian schools for the benefit of U S P H S officers, both regular and reserve.

The Subcommittee on Surplus Medical and Hospital Supplies reported that the U S Public Health Service had drawn up a plan for the disposal of surplus medical supplies. This Subcommittee was instructed to review the plan and to report back to the Central Committee with recommendations. Dr George Morris Piersol, F A C P, was appointed a member of this Subcommittee.

There were progress reports from Subcommittees interested in Educational Assistance for Veterans through the Veterans Administration, the Establishment of a Medical Corps in the Veterans Administration, Sources of Funds to be used for Post-war Medical Education, the status of the Army Specialized Training Program and the Navy V-12 Program, and matters of a kindred nature.

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#### NEWS FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

Major General Norman T Kirk, F A C P, The Surgeon General, and Brigadier General James S Simmons, F A C P, Chief of the Preventive Medicine Service, completed a six weeks' tour of the Pacific Theater of Operations during February and March.

Lt Col Raymond G Hussey, F A C P, Director of the Army Industrial Hygiene Laboratory, Baltimore, has retired from active duty to accept an appointment as Dean

of the School of Occupational Health, which he is now organizing at Wayne University, Detroit Col Hussey is one of the foremost authorities in the field of occupational health His development of the Army Industrial Hygiene Laboratory, under the Preventive Medicine Service, represents a new departure in this field of preventive medicine in the U S Army At Wayne University he will organize the first formal program of educational health and medicine

Col C C Odom, F A C P, is the Commanding Officer of the Mason General Hospital, Long Island, N Y, where a three months' course in Military Neuropsychiatry is being given, in conjunction with Columbia and New York Universities

Lt Col Burgess L Gordon, F A C P, of Philadelphia, has been transferred from the Technical Division, Operations Service of the Office of the Surgeon General to the U S Army General Hospital, Camp Pickett, Va

Brigadier General Hugh J Morgan, F A C P, Consultant in Medicine to the Surgeon General, has been elected a member of the Endowments and Grants Committee of the Army Medical Library Dr Arthur H Sanford, F A C P, of the Mayo Clinic, is also a member of this Committee

Major Douglass W Walker (Associate), Executive Officer, Preventive Medicine Service, Office of the Surgeon General, has been promoted to the rank of lieutenant colonel

Major General George F Lull, F A C P, Deputy Surgeon General, is President of the Medical Research Board in the Office of the Surgeon General, the purpose of which is to coordinate all medical department research with other staff agencies and components of the Army, as well as with agencies outside the Army Lt Col Leon H Warren, (Associate), Chief of the Research Coordination Branch, Technical Division, Operations Service, is recorder

#### *Recent Promotions, Medical Department Officers*

Major to Lieutenant Colonel J Warren Hundley, Jr, F A C P, Philadelphia, Pa, Edward G Thorp, F A C P, Melrose, Mass, Algot R Nelson, F A C P, Grand Rapids, Mich, James E Cottrell, F A C P, Philadelphia, Pa, Harold A Golz, F A C P, Clarksburg, W Va, Raymond L Barrett, F A C P, Longmeadow, Mass, Hiland L Flowers, F A C P, Bronx, N Y, Douglas M Gordon, F A C P, Ponca City, Okla, T Douglas Kendrick, F A C P, Utica, N Y, Charles Stuart Wilson, F A C P, Detroit, Mich

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Dr Charles E Leonard, (Associate), who formerly was Assistant in Medicine at the University of Oklahoma School of Medicine, has been appointed Instructor in Psychiatry

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Dr Dwight O'Hara, F A C P, Acting Dean and Professor of Preventive Medicine, Tufts College Medical School, Boston, was the first speaker on a Graduate Seminar in Industrial Health, Brown University, Providence, February 20, his subject being "Bases of Industrial Medical Practice"

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Dr Paul Brindley, F A C P, Galveston, Dr May Owen, F A C P, Fort Worth and Dr John J Andujar, F A C P, Fort Worth, were elected President, President-elect, and Secretary-Treasurer, respectively, at the Annual Meeting of the Texas Society of Pathologists during January

The New York Heart Association, which heretofore has been a part of the New York Tuberculosis Health Association, has separated from the latter organization and will continue as an independent society, with headquarters in the building of the New York Academy of Medicine. Dr Edwin P Maynard, Jr, F A C P, Brooklyn, is President of the Association, Dr Harold E B Pardee, F A C P, is Chairman of the Finance Committee

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Col Marion H Barker, F A C P, of Chicago, recently received the Legion of Merit "for exceptionally meritorious conduct in the performance of outstanding services in the North African Theater of Operations, from January 21, 1944, until July 8, 1944. Assigned to the study of infectious hepatitis, Col Barker devised a comprehensive and effective plan of investigation and discovered valuable new data concerning its diagnosis, progress, treatment and after-effects. By his keen scientific insight and coordinated labors, he developed methods of treatment and criteria for the disposition of patients suffering from this disease, which prevent undue damage and restore most of those afflicted to their normal activities as healthy individuals, rather than as chronic sufferers. The fighting strength of the Army has been measurably increased by this work. The investigations conducted by Col Barker are among the outstanding contributions to medical science during this war and are consistent with the highest traditions of research in the Medical Corps of the Army"

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Major General George F Lull, F A C P, Deputy Surgeon General, U S Army, gave the principal address, "Some Wartime Problems of the Medical Department and Some of Its Accomplishments," on the occasion of the 75th anniversary of the Raleigh (N C) Academy of Medicine, February 2

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"Wartime Medical Research" was the title of the annual Walter L Niles Memorial Lecture, by Dr Edwin Cowles Andrus, F A C P, Baltimore, at Cornell University Medical School on February 20

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The name of the Hamilton County (Ohio) Tuberculosis Hospital, Cincinnati, was recently changed by the Board of Trustees to the "Dunham Hospital" in honor of the late Henry Kennon Dunham, F A C P, who served as its Medical Director from 1914 to 1941

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Rear Admiral Edward R Stitt, F A C P, (MC), U S N, Retired, former Surgeon General of the U S Navy, was the recipient of a gold medal and an honorarium of \$500 for outstanding service in the field of tropical medicine, presented by the American Foundation for Tropical Medicine on February 5

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Col Harry G Armstrong, F A C P, (MC), U S A, was recently awarded the Legion of Merit for exceptionally meritorious conduct in the performance of services from September 8, 1939, to June 20, 1941

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Major General Shelley U Marietta, F A C P, (MC), U S A, although having reached the statutory retiring age, will be retained as Commanding General of the Walter Reed General Hospital in Washington

Dr Charles J Bartlett, F A C P , Emeritus Professor of Pathology, Yale University School of Medicine, recently celebrated his 80th birthday as guest of honor at a dinner tendered by the New Haven Medical Association

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Dr J Arnold Bargen, F A C P , Associate Professor of Medicine University of Minnesota Graduate School, delivered the 24th Annual Beaumont Lecture of the Wayne County Medical Society, Detroit, February 19 on "Modern Concepts of Intestinal Infection"

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Dr Kail D Figley, F A C P , Toledo, has succeeded Dr Will Cook Spain, F A C P , New York City, resigned, as Secretary of the American Academy of Allergy. The Academy has built up a fund to constitute an annual Secretary's Prize, and the first recipient of this prize was Dr J Harvey Black, F A C P , Dallas, Tex , for his paper, "The Treatment of Urticaria with Synthetic Vitamin K"

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The art contest, sponsored by Mead Johnson & Company, "Courage and Devotion Beyond the Call of Duty," has not been cancelled or postponed. The closing date remains May 27, 1946

There will be no annual exhibit in 1945 of the American Physicians Art Association, however. For full details regarding the \$34,000 in prizes, address the Secretary, American Physicians Art Association, Flood Bldg , San Francisco, Calif

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#### PERMANENTE FOUNDATION RESEARCH FELLOWSHIPS

The Permanente Foundation will offer a limited number of Fellowships for Clinical Research in the fields of medicine, surgery and related specialties. Research Fellowships in the field of internal medicine are announced for investigations in "Cardiac Status in Pneumonia" and "Evaluation of Recent Advances in Peptic Ulcer Therapy"

The Fellowships provide \$225 monthly, plus maintenance. For information, address Chairman, Fellowship Committee, Permanente Foundation Hospital, Oakland 11, Calif

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Capt B W Hogan, F A C P , (MC), U S N , was recently assigned as Senior Medical Officer on the new hospital ship, U S S *Tranquility*. The ship is air conditioned throughout and equipped with the finest of medical and surgical facilities. It has 802 permanent beds

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The Society for Investigative Dermatology announces the resumption of publication of their periodical, the *Journal of Investigative Dermatology*, which temporarily suspended publication in 1942 on account of war conditions. The first number of Volume 6 appeared in February. It will be issued bi-monthly, one volume a year, at \$6.00 per volume, by The Williams and Wilkins Company, Baltimore 2, Maryland

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#### CORRECTION

ANNALS OF INTERNAL MEDICINE, February, 1945, page 327, paragraph 2. "There was an urgent request for the repetition of this course (Cardiology, Boston Dr Paul D WHITE, Director) this coming winter or spring, but Dr White was so 'busy' (not 'exhausted') that he has asked to have the repetition of the course delayed at least until the autumn of 1945"



## WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 3 (New York)—Dr O R Jones, Chairman, Dr N Jolliffe, Dr H W Cave

*Induction Center, Grand Central Palace, New York, New York*

April 20 Common Wartime Dermatoses—Dr Frank C Combes

April 27 (to be repeated on May 4) Common Allergic Manifestations—Dr Joseph Harkavy

May 11 (to be repeated on May 18) Deleterious Effects of Drugs on the Hemopoietic System—Dr Nathan Rosenthal

May 25 Deficiency States and Their Recognition—Dr H D Kruse

REGION No 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr B P Widmann, Chairman, Dr J S Rodman, Dr S P Reimann

*U S Naval Hospital, Philadelphia, Pennsylvania*

April 20 Subject to be announced—Dr George Wilson

May 4 Subject to be announced—Dr Frank Adler

May 18 Health Department Military Liaison in Venereal Disease—Dr Norman Ingraham

REGION No 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr J A Lyon, Chairman, Dr C R Edwards, Dr C B Conklin

*Regional Hospital, Camp Lee, Virginia*

April 20 Evaluation of the Surgical Risk and Anesthesia—Captain William A Weiss

April 27 Prevention and Treatment of Wound Infections with Sulfonamides—Captain James E T Hopkins

*Newton D Baker General Hospital, Martinsburg, West Virginia*

April 16 Psychosomatic Medicine—Dr Claude L Neale  
Recent Developments in Nutrition—Dr J C Forbes

May 7 Neuro-Surgical Clinic—Dr Charles Bagley, Jr  
Chemotherapy in Dysentery—Dr Lay Martin

May 21 Narcosynthesis and Hypnoses—Dr Addison McGuire Duval  
Peripheral Vascular Diseases Due to War-Time Conditions—Dr J Ross Veal

*A A F Regional Hospital, Langley Field, Virginia*

April 27 Psychosomatic Medicine—Dr Solomon Katzenelbogen  
Radiology—Dr Frederick M Hodges

May 25—Aviation Medicine—Dr L G Lederer  
Fundamentals of Plastic Surgery—Dr Robert E Moran

REGION No 8 (Western Pennsylvania, Ohio)—Dr C A Doan, Chairman, Dr P G Smith, Dr F M Douglass

*Criple General Hospital, Cleveland, Ohio*

April 24 Congenital Anomalies of the Genitourinary Tract—Dr William E Lower

REGION No 14 (Indiana, Illinois, Wisconsin)—Dr W O Thompson, Chairman, Dr N C Gilbert, Dr W H Cole, Dr W D Gatch, Dr R M Moore, Dr H M Baker, Dr E R Schmidt, Dr E L Sevringhaus, Dr F D Murphy

*Gardiner General Hospital, Chicago, Illinois*

- April 25 Endocrinology
- May 2 Virtus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
- May 16 Mental Hygiene and the Prevention of Neuroses in War
- May 23 Wound Healing and Tendon Surgery

*Station Hospital, Fort Sheridan, Illinois*

- April 25 Psychosomatic Medicine
- May 2 Wound Healing and Tendon Surgery
- May 16 Peptic Ulcer, Gall Bladder and Liver Diseases
- May 23 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases

*Mayo General Hospital, Galesburg, Illinois*

- April 25 Mental Hygiene and the Prevention of Neuroses in War
- May 2 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases
- May 16 Chest Diseases and Diseases of the Larynx
- May 23 Low Back Pain

*Vaughan General Hospital, Hines, Illinois*

- April 25 Peptic Ulcer, Gall Bladder and Liver Diseases
- May 2 Low Back Pain
- May 16 Heart Disease and Allied Conditions
- May 23 Bone and Joint Infections

*Station Hospital, Camp Ellis, Illinois*

- April 25 Chest Diseases and Diseases of the Larynx
- May 2 Bone and Joint Infections
- May 16 Arterial Vascular Disease—Traumatic Lesions
- May 23 Repair of Bone in Fractures and Diseases

*Station Hospital, Chanute Field, Illinois*

- April 25 Conditions Affecting Glucose Metabolism
- May 2 Plexus and Peripheral Nerve Injuries
- May 16 Dermatological Diseases
- May 23 Burns and Plastic Surgery

*Station Hospital, Camp McCoy, Wisconsin*

- April 25 Heart Disease—Dr Chester M Kurtz
- May 2 Repair of Bone in Fractures and Diseases
- May 16 Diseases of the Kidneys—Urogenital Tract
- May 23 Blood Dyscrasias, Malaria, Filariasis

*Station Hospital, Truax Field, Wisconsin*

- April 25 Diseases of the Kidneys—Urogenital Tract—Dr Francis D Murphy
- May 2 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment
- May 16 Conditions Affecting Glucose Metabolism
- May 23 Brain and Spinal Cord Injuries

*Billings General Hospital, Indiana*

- April 25 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care
- May 2 Burns and Plastic Surgery
- May 16 Malignancies in the Army Age Group—Medical X-Ray and Surgical  
Diagnosis and Treatment
- May 23 Endocrinology

*Wakeman General Hospital, Indiana*

- April 25 Dermatological Diseases
- May 2 Endocrinology
- May 16 Virus and Rickettsial Diseases—Medical and Neurological Diseases and  
Treatment
- May 23 Psychosomatic Medicine

REGION No 23 (Nevada, Northern California)—Dr S R Mettier, Chairman,  
Dr E H Falconer, Dr D N Richards

*Station Hospital, Hamilton Field, California*

- May 2 Early Post-Operative Ambulation of Surgical Patients—Dr H Glenn Bell
- May 16 Fractures of the Extremities—Dr Carl Anderson
- May 30 Diagnosis and Treatment of Arthritis—Dr Stacy R Mettier

*Station Hospital, Camp Roberts, California*

- April 21 Psychosomatic Medicine—Dr Douglas G Campbell
- May 19 Diagnosis and Treatment of Arthritis—Dr Hans Waime
- May 26 The Treatment of Poliomyelitis—Dr Henry D Brainerd

*Station Hospital, Chico Army Air Base, California*

- April 19 Diagnosis of Deficiency Diseases—Dr James F Rinehart
- April 26 Newer Methods of Treatment of Heart Disease—Dr Francis Chamberlain

REGION No 24 (Southern California)—Lt Comdr G C Griffith, Chairman, Capt  
H P Schenck, Dr W A Morrison, Dr J F Churchill

*Station Hospital, U S Naval Air Training Station, San Diego, California*

- April 20 Treatment of Syphilis with Penicillin—Major Paul Recque

*A A F Regional Hospital, Santa Ana, California*

- April 17 Surgery of the Traumatic Abdomen—Dr Charles Phillips and Commander  
Gaylord Bates

*Station Hospital, March Field, Riverside, California*

- April 17 Blood Plasma and Blood Substitutes—Lieutenant Colonel R M Jones  
Water Balance—Major Edward Schwartz

## ANNUAL FINANCIAL STATEMENT

## THE AMERICAN COLLEGE OF PHYSICIANS, INC

December 31, 1944

The following statements are taken from the report of the Auditor, December 31, 1944, and are published for the information of Fellows and Masters

*Balance Sheet*

## General Fund

*Current Assets*

Cash in Bank and on Hand	\$ 39 618 80	
Accounts Receivable	2,669 09	
Inventory of Keys, Pledges and Frames	451 70	
Accrued Income on Investments	1,893 93	
Investments at Book Value	122,389 10	
Insurance Deposit	555 00	\$167,577 62
		<hr/>

*Fixed Assets*

Real Estate	\$ 58,898 95	
Furniture and fixtures	\$11,111 20	
Less Depreciation	8,691 08	2,420 12
		<hr/>
TOTAL ASSETS, General Fund		\$228,896 69

*Liabilities**Current*

Accounts Payable	\$ 621 01
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*Deferred Income*

Advance Subscriptions, ANNALS OF INTERNAL MEDICINE	17,305 50
Philadelphia Postgraduate Fund, Reserve	2,284 30
	<hr/>

TOTAL LIABILITIES, General Fund	\$ 20,210 81
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PRINCIPAL, General Fund	\$208,685 88
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*Balance Sheet*

## Endowment Fund

*Current Assets*

Cash in Bank	\$ 10,233 61
Investments at Book Value	157,509 78
Due from Brokers	2,000 00
	<hr/>

PRINCIPAL, Endowment Fund	\$169,743 39
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TOTAL PRINCIPAL, Both Funds	\$378,429 27
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	<i>Jan 1, 1944</i>	<i>Dec 31, 1944</i>	<i>Net Increase</i>
General Fund	\$208,076 48	\$208,685 88	\$ 609 40
Endowment Fund	146,724 54	169,743 39	23,018 85
	<u>\$354,801 02</u>	<u>\$378,429 27</u>	<u>\$23,628 25</u>

## SUMMARY OF OPERATIONS

Year Ending December 31, 1944

*General Fund**Income*

Annual Dues	\$ 23,100 56	
Initiation Fees	5,350 50	
Subscriptions, ANNALS OF INTERNAL MEDICINE	37,868 99	
Advertising, ANNALS OF INTERNAL MEDICINE	13,279 83	
Subscriptions, ANNALS OF CLINICAL MEDICINE	14 87	
Income from Investments, Endowment Fund	5,362 50	
Income from Investments, General Fund	5,604 43	
Dividend on Perpetual Insurance Deposit	60 00	
Sales of Miscellaneous Publications	6 43	
Rent, Net, 404-12 S 42nd Street	723 05	
	<u></u>	
TOTAL, Income		\$ 91,371 16

*Expenditures*

Salaries	\$ 25,350 98	
Postage, Telephone and Telegraph	3,891 36	
Office Supplies and Stationery	1,241 36	
Printing	25,741 36	
Traveling Expenses, Executives, Committeemen, Regents	2,829 51	
Miscellaneous	1,495 46	
College Headquarters		
Maintenance	\$3,330 83	
Heat, Light, Gas and Water	779 76	
Taxes	170 77	
Insurance	85 05	4,366 41
	<u></u>	
Depreciation on Building	\$1,000 00	
Depreciation on Furniture and Fixtures	833 04	1,833 04
	<u></u>	
Investment Counsel and Custodian Fees	472 18	
Regional Meetings	2,574 83	
1944 Postgraduate Courses	1,071 50	
War-Time Graduate Medical Meetings	5,000 00	
Collection and Exchange Fees	22 74	
Loss on Sale or Maturity of Investments	970 81	
1944 Supplement	330 02	
Keys, Pledges and Frames	123 96	
1944 Annual Meeting of Officers, Regents and Governors	7,395 41	
	<u></u>	
TOTAL, Expenditures		\$ 84,710 93
		<u></u>
NET INCOME, Year Ending December 31, 1944		\$ 6,660 23

General Fund Balance, January 1, 1944	\$208,076 48	
Less Transfer to Endowment Fund of Initiation Fees of New Life Members	6,035 00	
Transfer to Subscriptions, ANNALS OF INTERNAL MEDICINE	15 83	202,025 65
PRINCIPAL, General Fund		<u>\$208,685 88</u>

*Endowment Fund*

Endowment Fund Balance, January 1, 1944	\$146,724 54	
Add Life Membership Fees Received During 1944	17,223 00	
Initiation Fees of New Life Members Trans- ferred from General Fund	6,035 00	
Transfer of Dues of New Life Members	182 00	
Profit on Sale of Endowment Fund Investments	1 87	
	<u>\$170,166 41</u>	
Less Loss on Sale of Endowment Fund Investments	423 02	
PRINCIPAL, Endowment Fund		<u>\$169,743 39</u>

*OBITUARIES*

## DR BERTNARD SMITH

The death occurred recently in Los Angeles of Dr Bertnard Smith, F A C P, for many years one of the outstanding members of the profession in that city

Dr Smith was born in Tyler, Texas in 1877, but spent most of his early life in Galesburg, Ill, graduating from Knox College in 1898. He received his degree in Medicine from Rush Medical College in 1903 and interned at the Presbyterian Hospital in Chicago, Illinois from 1904 to 1906. Later on he did Postgraduate Study at the University of Heidelberg, the University of Vienna and in 1914 at Harvard University, where he worked with Professor Otto Folin at the time that modern clinical methods applicable to chemical studies of the blood and urine were being developed. He served with the United States Army Medical Corps during World War I and during that time was closely associated with a group which had been organized for the study of cardiovascular disorders, especially neurocirculatory asthenia, being part of the time personally in charge of this investigation.

Dr Smith had come West immediately following his internship and settled in Los Angeles. After he resumed his private practice in 1919 his chief interest became the care and treatment of diabetes. At a time when insulin still was expensive and difficult to obtain he was able, by soliciting private donations from friends, to supply a fairly large group of patients who were in serious need. Later he helped create the non-profit organization, Los Angeles Metabolic Clinic. He always was particularly concerned

in aiding the younger patients in mastering their problem and becoming self-supporting, and was for years a guiding influence of the Diabetic Service at Children's Hospital. He also organized the very fine Diabetic Clinic at the Cedars of Lebanon Hospital.

During his many years in Los Angeles he had become a member on the staffs of the Children's and Cedars of Lebanon Hospitals and a Life Member of the staff of the Hospital of the Good Samaritan. For a number of years he was Clinical Professor of Medicine at the University of Southern California School of Medicine. He was a member of the Los Angeles County Medical Association, the California Medical Association, the American Heart Association, the American Society for Clinical Investigation and a Fellow of the American College of Physicians.

Dr. Smith was a kindly, courteous man, wholly unselfish, seeking neither personal preferment nor financial gain. His place in the profession will not be easily filled and he leaves many close friends and faithful patients.

He is survived by his wife, Marion Macneil Smith, and one daughter, Mrs. Wilson Phelp.

ROY E. THOMAS, M.D., F.A.C.P.  
Governor for Southern California

#### DR. GEORGE ALLEN RICKETTS

Dr. George Allen Ricketts, F.A.C.P., Osceola Mills, Pa., died December 6, 1944, of cerebral embolism, at the age of seventy-one. Dr. Ricketts was born at Flinton, Pa., August 17, 1873. He held the degree of Master of Education from the Pennsylvania Central State Normal School. He graduated in medicine from Jefferson Medical College of Philadelphia in 1908, and did some postgraduate work at Harvard Medical School.

At one time he was a member of the staff of the Miners' Hospital, Spangler, Pa., and for many years Chief of the Medical Staff of the Philipsburg State Hospital.

Dr. Ricketts was a member and former President of the Clearfield County Medical Society, member of the Pennsylvania Medical Society and the American Medical Association, Fellow of the American College of Physicians since 1931. He retired from the practice of medicine in August, 1940, because of coronary thrombosis.

# ANNALS OF INTERNAL MEDICINE

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NUMBER 5

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## HEART DISEASE IN THE JUNGLES OF THE SOUTH PACIFIC SOME OBSERVATIONS MADE AMONG THE MELANESIANS OF THE NEW HEBRIDES AND SOLOMONS ISLANDS AREA \*

By ALBERT SALISBURY HYMAN, F A C P , Commander (MC), USNR

### PREFACE

IN the spring of 1942 a new page was written into the history of United States naval warfare, the technic of "island hopping" was being developed in the South Pacific theatre of the war. As island after island of the New Hebrides and Solomons groups was wrested from enemy control, the plan of occupation called for perfect timing and teamwork between marine combat fighting units, naval construction battalions, and the task force land based staff which included the medical, communications, and supply stations. From out of wild jungle terrain there were hacked almost over night temporary landing strips and huge air fields for the fighting and supply planes. The change from the isolated solitude of some of the most primitive spots in the world to the tumultuous traffic of a busy international airport occurred in an unbelievably short time.

Although mechanized equipment played a great rôle in the building of these tremendous projects, manual labor was needed to complete many tasks. It became necessary to supplement the regular naval personnel with laborers selected from the native Melanesian population of the islands. An experiment with an initial group of about 45 youths and men drawn from various tribes and settlements showed them to be cheerful and willing workers with a remarkable ability to learn by imitation, by carefully watching the actions of the instructor, it required but little time and patience for most of the natives to become adept with the pick and shovel, hammer and saw, and even with some mechanical tools.

\* Received for publication January 6, 1945

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

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The success of this native labor venture led to the development of a larger plan to establish complete battalions of Melanesians from the various islands of the New Hebrides and Solomons groups. A special recruiting unit was set up to visit the more thickly populated areas in order to select the candidates for this native labor battalion. This unit consisted of naval officers from construction battalions, interpreters, medical officers, corpsmen, and a few French colonists who were familiar with the islands situation. It was my good fortune to have been the Senior Medical Officer of the party.

Experience soon taught that the value of any given native in such a labor battalion was in direct proportion to his health and his freedom from the multitude of tropical diseases prevalent throughout this area of the South Pacific. Malaria, amebic dysentery, dengue, hookworm, yaws, tsutsugamushi fever, filariasis, and the fungus infections are but a few of the more common disabling conditions which were found among the Melanesians of nearly every island. For this reason, every candidate was given a more or less complete physical examination before he was subjected to other tests to determine his desirability as a member of the labor unit, many could be screened out on mere inspection whereas others were again carefully examined before they were finally admitted to the native compound near the work project.

Although the recruiting party was primarily interested only in young able bodied men, it soon became evident that much good will was engendered by paying some medical attention to women and children, and it was not long before whole settlements would turn out for examination whenever we arrived at a new location. An opportunity was thus given to see several hundred natives, some from extremely primitive groups not far removed from the headhunters of Malakula and other savage islands.

While the natives presented many other medical problems, I was especially interested in the various cardiovascular diseases which were discovered, for here I had an opportunity of investigating the development of certain heart and blood vessel conditions free from the so-called pernicious rôle of modern civilization with its continuous emotional stress, highly refined foods, lack of exercise, alcohol, tobacco, drugs, and the host of other alleged evils. If the current belief that the high incidence of heart disease is the result of a way of living, then these Melanesians in their jungle paradise should be relatively immune to such conditions as high blood pressure, arteriosclerosis, coronary heart disease, and peripheral vascular disturbances.

#### ARTERIOSCLEROSIS

One of the most striking early observations about these people of the jungle is the general absence of very old individuals with gray hair, the explanation was simple. Longevity is not the rule in the jungle, either among men or beasts. The oldest persons seen were among the women, calculated from the native scheme of determining time (lunar calendar),

they were about 55 to 58 years old. The oldest men were said to be about 50. After the age of 18 most individuals appeared to be from 10 to 20 years older than their actual age.

The incidence of obvious arteriosclerosis was high in those of 30 and older, prominent and tortuous temporal arteries was a common sight in nearly all of these. The radial arteries were thickened and rigid and the dorsalis pedis was difficult to palpate in many. The beaded type of calcification was less common than the generalized, but some of the older women showed the Pal-Winterberg form of arterial sclerosis. Oriental cataract is frequent and the natives readily permitted fundus examination, but they did not take kindly to nose and throat or ear investigation. Changes in the retinal vessels appeared early in life, some were rather extreme.

One gained the impression that vascular degenerative pathologic lesions started earlier in these Melanesians than in comparative groups of Americans or Europeans, this was particularly true of the peripheral vascular disturbances. I shall have occasion to speak more fully of this at a later time.

#### BLOOD PRESSURE

In general, no objection was made to the taking of blood pressure, the natives wear several ornamental arm bands which frequently are so tight that there is considerable edema below the constricting rings. Inflation of the blood pressure cuff never failed to cause them amusement and they were fascinated by the movements of the manometer needle. There were some differences in the pressures of individual groups on the various islands, a certain large settlement was found to have a number of persons with rather low levels: 80–90 mm Hg systolic and 40–50 mm diastolic. On other islands the blood pressure levels were more or less similar to those of Americans of equal age, weight, and sex.

Of no little interest, however, were the findings on three islands which were some distance from each other. A group of individuals, both men and women, had rather high systolic blood pressure levels: 180–235 mm Hg systolic to 96–115 mm diastolic. In one tribe which consisted of a much inter-married family, 11 persons out of 19 over the age of 30 who were examined had elevated systolic pressures. In this same settlement a boy of about 18 had a blood pressure of 160 mm Hg systolic and 104 mm diastolic. These groups of hypertension were worthy of far more study and attention than it was possible to give, the non-medical members of the recruiting party were naturally interested only in healthy natives and any time devoted to those who could not meet the required physical standards was considered in a good natured way as holding up the war effort. Thus only a most cursory examination of these hypertensive cases was possible.

Outside of the factor of consanguinity, there did not appear any other reason for the higher blood pressure levels in these Melanesians than in their neighbors on nearby islands. The problems of food, climate, exposure to

tropical infestation, and environment are about the same on all of the islands visited. Why, then, the hypertensive syndrome in these few isolated settlements? A provocative suggestion came from one of the French colonial plantation owners who had lived in this part of the tropics for more than 30 years and who seemed to have a veritable storehouse of information concerning the South Pacific. He said that there was a current belief among the Native Practitioners that black water fever was frequently followed by hypertension. He was patient enough to question at some length, in the various dialects of pidgin English, nine of the Melanesians who had high blood pressure and found in six a more or less definite history of hematuria or the passing of very dark colored urine during an especially severe episode of chills and fever which had been treated with quinine.

Black water fever was not a common complication among the combat personnel during the early days of the Solomons campaign, I have previously reported<sup>1</sup> that from October 1942 up to May 1943 several thousand cases of malaria were seen at a certain advanced base hospital with a very small incidence of the condition. The follow-up of some of these cases has not shown any permanent renal damage. The available literature upon black water fever does not mention hypertension as a possible sequela to the condition and there is but vague reference to late kidney disease in these cases. This is still one of the great unexplored problems associated with malaria control but I have the unproved impression that certain tropical diseases may be productive of hypertension as the secondary result of renal damage.

Another interesting side light was obtained in regard to the incidence of high blood pressure among these Melanesians, pre-eclamptic toxemia is apparently not unknown. I was told that in a prominent tribal family nearly all of the women had experienced this difficulty and that there had been two deaths.

The end result of long standing hypertension was seen in two individuals who had suffered hemiplegia, the interpreters said that apoplexy was known to the natives who have a special word for one-sided paralysis *nomuffaf* which may be the contraction of "no move half". Pidgin English has many such contractions of two or more words.

#### CARDIAC HYPERTROPHY

We were all impressed by the number of hearts which seemed to be enlarged by simple percussion and inspection, roentgen-ray was not available in the field but several natives were subsequently examined at the advanced base hospital and they all had a general cardiac hypertrophy without any other signs of heart disease. Eleven men were accepted in the labor unit all of whom had evidence of enlarged heart, the apex impulse was in the sixth interspace and outside of the midclavicular line but they presented no other clinical indications of cardiovascular impairment. Reexamination

several months later after they had completed their work and were being returned to their home islands showed no change

### IRREGULARITIES OF THE HEART

*Tachycardia* with rates as high as 160 was not uncommon during the first examination of these men, later the rates were easily controlled by vagal respiratory tests. The native Melanesians apparently have a very labile and responsive autonomic system, the exercise test was usually exaggerated but much of this was psychosomatic. When they became accustomed to the company of the Americans and to the medical personnel, all of their reactions became less violent and more controlled but some continued to have accelerated pulse rates during the several months that they were under observation. I saw no evidence of hyperthyroid disease and goiter is unknown.

An *extrasystolic arrhythmia* was discovered in a few individuals, both men and women, these premature contractions also appeared to be chiefly psychosomatic, but some of the natives said that they had experienced heart consciousness for a long period of time. This was described in a variety of ways, but the hand was invariably placed over the precordium as they discussed the matter with the interpreter.

Only one case of *auricular fibrillation* was discovered, but the Chief Native Practitioner said that he had seen several, he spoke of *delirium cordis* and said that it occasionally occurred during the course of some of these severe tropical fevers. He had also seen a number of cases of *paroxysmal tachycardia*. These had been chiefly among the women and especially during their climacteric, no explanation was given in regard to this unusual occurrence of the condition. There apparently had been no disastrous results and they all had gotten well.

### MURMURS

A great number of murmurs were heard, these were largely *systolic* in time and were more or less localized over the pulmonic valvular area. They had the characteristics of so-called functional pulmonic systolic murmurs and were not associated with any other obvious cardiovascular disease. This murmur appeared in equal frequency in all age groups examined and in many thin individuals the murmur was loud enough to be evaluated as grade 2 or 3. The possibility of some vague tropical infection of the pulmonic valve or artery was considered but there was no evidence of other signs and symptoms associated with syndromes like Ayerza's disease.

*Apical systolic murmurs* were also quite frequent, these showed the usual changes in quality and duration depending upon posture, exercise, and breath holding. They were all classified as functional and were not associated with any other signs of heart disease, in a few men with hyper-

troubled hearts, however, this murmur was regarded with some suspicion but there was no proof that the combination was not purely coincidental

*Aortic diastolic murmurs* were the most common of the group considered to be pathologic, these cases were discussed at some length with the Native Practitioners. Several investigations have been made at the Fiji Medical School and at the Royal French Hospital at Noumea, New Caledonia concerning the syphilis-like infections occurring in the South Pacific jungles. Yaws, tropical leprosy, and chronic tsutsugamushi disease are but a few of the various conditions which simulate syphilis in certain pathologic processes. In addition, several tropical fevers like malaria, dengue, and sand fly fever frequently cause positive Kahn serological reactions. The rôle of syphilis in producing specific types of aortitis is now well established, retrograde extension of the process is responsible for late involvement of the aortic valves and severe grades of aortic insufficiency are a common manifestation of tertiary syphilis.

There is apparently some disagreement of opinion in regard to the incidence of syphilis among the native Melanesians of these islands, the French Hospital authorities at Efati declared that the last survey made in 1935 showed a relatively high degree of population infection. Dr Aisiri of the Fiji Medical School thought that the rate was rather low in comparison with certain southern states of this country. Other manifestations of tertiary syphilis with central nervous system or bone and joint involvement are rare, tabes is more or less unknown among the Melanesians.

The etiology of these aortic diastolic murmurs is thus open to some speculation, unless they are due to a disproportionately high incidence of syphilitic vascular disease, they must be the result of certain tropical infections, particularly yaws and perhaps chronic tsutsugamushi disease. The literature on the subject is not convincing, but this should prove to be a fertile field for research in tropical medicine since the late effects of both these diseases may subsequently appear in returning servicemen who have acquired these conditions while in the South Pacific.

No *presystolic murmurs* were discovered, rheumatic fever, if it occurs, must be very rare among the Melanesians. This is in rather sharp contrast with its occurrence among the other great racial stock of the South Pacific—the Polynesians. At Pago Pago in the American Samoas, through the courtesy of Capt A. C. Dixon (MC) USN, I had the opportunity of examining several children with unquestioned rheumatic heart disease and two young women with mitral stenosis, one a native nurse at the Samoan Hospital.

Farther south, in New Zealand, the Maoris, who also come from pure Polynesian stock, have a relatively high incidence of rheumatic fever. At Dr Alfred Dreifuss's clinic at Auckland I was privileged to see a number of cardiac Maori children. Here the incidence of rheumatic fever appears to be just as great among the Polynesians as among the European white group.

In published data this rate is approximately that of Atlanta, Ga. The Polynesians of the northern hemisphere as represented by the Hawaiians likewise have considerable rheumatic infection. At Honolulu I saw a number of rheumatic hearts among the pure Hawaiian group and the pathologic picture was not unlike that seen in the southern part of the United States.

The question whether acute rheumatic fever and rheumatic heart disease occur in the South Pacific has currently been the subject of some discussion, several papers have recently been published by authors who are not in complete agreement. I would hesitate to add to the confusion but the answer must be considered in three categories since it concerns three different groups of statistics. In my experience based upon a superficial survey made during 23 months' stay in the Pacific area, I would say that the Melanesians have little or no evidence of rheumatic infection whereas the Polynesians have a relatively high rate. The third group consists of the American servicemen, who, coming from all parts of the United States, have brought with them their own community's specific rate of infection. I have previously reported<sup>2</sup> the incidence of rheumatic fever among navy and marine combat units at an advanced base in the South Pacific, in every instance there was a history of previous rheumatic infection. I did not see a single case of primary rheumatic fever, but there were many individuals who went through their second or third attack while in the tropics.

#### ANGINA PECTORIS AND CORONARY HEART DISEASE

In view of the general prevalence of arteriosclerosis, the incidence of acute coronary thrombosis appeared to be exceedingly low, only one case of acute occlusion was seen, but the Native Practitioners reported that the condition was diagnosed from time to time. It was more frequent among the Melanesians living along or close to the sea coast than in those tribes that had settlements far in the hinterland of the jungle. It had not been seen in the hypertensive group previously described and it was not a common cause of death. On the other hand, in most of the cases with congestive heart failure, particularly in the older age groups, this was said to be due to chronic coronary disease.

*Heart pain* is not a common symptom among the natives, five French plantation owners who formerly employed large numbers of Melanesians to operate the huge coconut and copra industries agreed that compared to the other numerous complaints, the natives rarely reported pain in the heart. The Native Practitioners likewise said that angina pectoris was practically unknown, cardiac symptoms when they occurred were either related to dyspnea or heart consciousness in the form of palpitation. During the time that the native labor battalion was under observation, no one appeared at the field clinic for the relief of heart pain, but there were a few cases of dyspnea.

*Congestive heart failure* with edema of the legs and ascites is, however,

well known to the Melanesians, indeed many of their carved wooden figures show large rounded abdomens and greatly swollen legs. The early witch doctors were familiar with a number of digitalis-like substances which grow abundantly in the jungle. The water onion of the squill family and certain forms of *Cactus grandaeflorus* are favorite remedies for the treatment of anasarca. A tropical variety of fox glove called *gnopa* or *opa-opa* is employed by some of the Native Practitioners, this should not be confused with *po-po* (paw paw) or papyia, the seeds of which are said to be dangerous to those suffering from dropsy. There are several kinds of nuts which have a digitalis action, some of these like *thevetin* from the oleander tree and *trakis* from the lantern nut have been studied in this country. Nature has thus provided the Melanesians with many effective drugs for the treatment of congestive heart failure and the jungle folk lore is replete with cures obtained by their use.

Time and circumstance did not permit the study these individuals merited, the etiology should be more carefully investigated. Although a number of cases were probably the end result of advanced aortic valvular insufficiency, most were due to chronic coronary heart disease, the Native Practitioners estimated the ratio to be from 1 to 3 or 1 to 4. Some of this opinion was based upon postmortem material. The ritual of burial (clenuded) in certain tribes requires removal of the viscera and thus an opportunity for examination of the heart is given. The Fiji Medical School is noted for its well trained native physicians and their opinions have the respect of the entire South Pacific.\* I did not see any of these hearts but from description they apparently showed considerable arteriosclerotic and atheromatous pathologic change with associated myocardial disease—the scarring from old myocardial infarcts and, in a few instances, well defined aneurysmal dilatation of the heart wall.

The interesting problem here is the predominance of so-called silent coronary disease among these primitive peoples and the possible explanation of why similar types of disease are associated with so much pain in the more civilized communities of the world. It is not that these Melanesians are less sensitive to painful stimuli as will be shown later, indeed their reactions to pain are usually quite child-like. I have seen robust men cry out at the prick of a jungle thorn, and no attempt is made to conceal painful feelings. But they pass through extensive coronary episodes without much, if any, pain. Why?

The question is provocative and more than academic, the answer can only be speculative. The entire problem of heart pain has never been satisfactorily explained notwithstanding the voluminous literature upon the subject and the huge amount of experimental work which has been done in the past 25 years upon the unraveling of the complex neurogenic network which involves the heart and aorta. One of the perplexing enigmas of

\* See Dr. Samuel Lambert's splendid book, "A Yankee Doctor in Paradise"

internal medicine is the lack of correlation between coronary-cardiac pathologic lesions and the clinical symptoms produced by those lesions, two individuals with (apparent) identical lesions as the result of coronary disease may present entirely dissimilar clinical syndromes. This is especially true in regard to the pain factor.

In so-called "civilized communities" most patients suffer pain during a coronary episode, a few do not. Among the Melanesians the reverse is true, pain is not a conspicuous feature of the same disease, yet their threshold for painful stimuli is not unlike that of the average American or European. I will even go further, for the question of heart pain has always been of considerable interest to me. In an experiment to determine the relative skin, and bone and joint sensitivity of these natives, a group of very black negro members from a local CB unit volunteered to undergo the same tests, with the negroid habitus as a common denominator the experiment was a crude attempt to evaluate the pain response to the same stimulus in two groups of individuals: the one representing the product of modern civilization, the other from life in the jungle unaffected by the complexities and burdens of such civilization. The results of the experiment proved only one thing: there were no appreciable differences in the pain reactions of the two groups.

Superficially, therefore, civilization has done nothing to change the simple pain-mechanisms but *something* has been done to the deeper and more complicated receptor systems. What is this intangible factor which is responsible for the intense pain pattern in angina pectoris and acute coronary occlusion? Why is heart pain so much greater in the civilized individual and why is it more or less absent in these primitive peoples? What fields of research are opened by these questions? Can this *something* be psychosomatic in origin? We have but scratched the surface of the fundamentals of psychosomatic medicine. Modern civilization and psychosomatic phenomena go hand in hand, in a study of these Melanesians of the jungleland of the South Pacific may lie the key to a better and clearer understanding of many serious maladies which now afflict our communities. Of these, the degenerative cardiovascular diseases play the leading rôle in disability and death. From out of those steaming jungles, now the scene of warfare and bloodshed, may come the answer, let us hope, in a later, more peaceful world.

#### PERIPHERAL VASCULAR DISTURBANCES

Peripheral vascular disease is not unknown among the Melanesians, the pidgin word *dedfut* includes a variety of conditions involving the feet and lower legs. The natives regard any disabling condition that prevents them from walking as "dead foot." A number of tropical skin infestations produce ulcerations of the feet and great swelling occurs from the secondary infections and lymphangitis. Some of these extensive infections involve the veins and subsequently the arteries of the lower leg with massive thrombosis and occlusion. Gangrene of one or more toes is not uncommon and



occasionally the whole foot may be included in the process. I had the opportunity of examining two such legs which were amputated by Lieut Jean Poulchan of the French Colonial Service at the Native Hospital at Espiritu Santos.

In one, a man age about 26, there had been a long history of severe pain in the great toe and sole of the right foot, from time to time large ulcerations appeared over the entire foot. These would heal and later break down again. The pain finally became so continuous and so severe that the man voluntarily begged Dr Poulchan to cut off the foot notwithstanding the native prejudice against dismemberment of the body because of ritual tabu. The foot was so edematous that no pulsation could be felt in the *dorsalis pedis* but the posterior popliteals seemed to be normal. The leg was removed just below the knee. Dissection of the leg showed the artery and veins completely obliterated by dense scar tissue which bound the entire contents of the sheath together like a thick cord. Even the severed ends of the arteries showed considerable sclerosis of the walls and much reduced lumina. The bones of the foot were atrophied and there seemed to be an extensive type of proliferative osteoarthritis involving the whole ankle joint.

The other case was less severe, this man was about 35 years old with a very long history of pain in the lower leg and toes, perhaps of 10 years' duration. Trophic ulcerations had occurred several times and healed slowly. At the time the leg was amputated there were only a few open skin areas but the pain was becoming unbearable. On examination there was no *dorsalis pedis* pulsation on either foot. All of the peripheral arteries appeared to be prematurely thickened and sclerosed, the blood pressure was normal. The man was very loquacious about the foot. "Dedfut he too damn much burn-burn, sam time slep no-no much lon-lon. Cartem oop off." (The sick foot now is paining me like it was burned all over but at the same time it feels as if it was asleep for a long time. Cut it off as you would cut off the foot of an animal.) Amputation was performed just below the knee, dissection here showed a chronic inflammatory process involving the artery and veins in the sheath. There was some obliteration of the lumen of the artery but the veins were completely occluded. Grossly, the condition resembled a type of Buerger's disease, but the possibility of a chronic suppurative pathologic process with secondary vascular changes could not be eliminated without better laboratory facilities than were available.

Dr Aisari, the Native Practitioner assigned by the Fiji Medical School for service in the New Hebrides, said that peripheral vascular disease was not uncommon but frequently it was so intimately associated with various tropical infestations of the feet that it was difficult to determine which condition was primary. The diagnostic evaluation of the pain factor was important, where the pain was out of proportion to the obvious degree of inflammatory changes, he always suspected an underlying vascular disturbance, since many badly infected feet had little or no pain. He thought,

however, that certain tropical infections might be responsible for vascular changes of the lower legs and feet and the secondary lowered resistance following the lessened blood supply completed the vicious circle ending in trophic ulceration and re-infection

*Varicose Veins* No account of the vascular diseases of the Melanesians would be complete without some comment upon the rather high incidence of varicosities of the lower extremities. Individuals of all ages, from children to the oldest, seemed to have some degree of venous disease. This may have been due to secondary changes in the veins of the lower legs as the late result of continuous re-infection of the feet by various tropical organisms. The natives use no protection for the soles of the feet and are bare footed throughout their lives. Although the soles of the feet are covered with an extremely thick cornified skin, the dorsum of the foot and the ankles have no such protection and are subject to scratching and cutting by coral and sharp spiculed jungle vegetation.

Here again it is difficult to determine the different steps in the evolution of the ulcerations, some seemed to be rather typical varicose ulcers, but others were better classified as tropical or jungle ulcers with a chronicity which obscures the basic disease. Many American servicemen developed ulcers of this kind as the result of trauma, usually by coral abrasion, with a secondary fungus infection. These presented a problem in therapy and in many instances the disability constituted a serious loss of front line manpower. The natives, however, regard these ulcerations with complete indifference and looked with some amusement when dressings were applied to keep the wounds clean, perhaps to some extent, they were right, for those ulcers which were kept clean and exposed to the sunlight seemed to fare as well as those treated by one combination of chemicals or another.

#### COMMENT

After our return to the advanced naval base from whence the recruiting unit started, I had an opportunity to go over the notes which I had made during the expedition through the various islands and to formulate certain opinions. The purpose of the trip has already been made clear and the territory covered, although extensive in itself, constitutes but a small part of the vast area west of the international date line and south of the equator known as "the South Pacific." The facts gathered and the impressions gained are thus predicated upon our own experiences and at best represent but a modest sampling of the Melanesian natives as we saw them in the island groups of the New Hebrides and Solomons. I would not want any statement made in this report to be construed as a final authoritative opinion upon any of the various conditions discussed. Such a report would necessitate a survey of much greater scope both in time and resources and over a considerable area not included in this expedition, such a survey would include the study of many more Melanesian groups—from the pigmies of

western Espiritu Santos to the giants of Matakanta, as well as the fabulous albinos of Bonokula

With these limitations in mind certain conclusions are, perhaps, permissible. First and foremost is the surprisingly high incidence of cardiovascular disease of all types found among these primitive peoples of the jungles, this is particularly true of the degenerative types of heart and blood vessel disease. I have used the word *surprisingly* for the conditions found were contrary to current thought and teaching. Throughout the literature upon arteriosclerosis, coronary heart disease, and hypertension is the constant repetition of the major rôle played by the stress of civilization in the development of these conditions. The psychosomatic reactions to business and social demands and the constant pressure of individual adjustment to a changing environment have been held responsible for the great increase in the cardiovascular degenerative diseases of the past several decades.

Yet the incidence of these very same diseases is also relatively high among a people whose entire life is more or less free from such alleged pernicious factors. To be sure, life in the jungle may be beset with a number of nature-made fears and man-made taboos but it is doubtful that the intensity of psychosomatic reaction to environment is anywhere as great among the Melanesians as among individuals in an average American community. What, then, can account for the development of these degenerative "civilized diseases" under a primitive way of living?

The jungle abounds with infections and infestations, in addition to the host of specific tropical diseases like malaria, yaws, tsutsugamushi fever, dengue, and sand-fly fever, all of the microorganisms known in the temperate zone thrive with unusual virulence in the tropics. Diphtheria, tuberculosis, meningococcus meningitis, pneumococcus pneumonia, tetanus, gas gangrene as well as the gastrointestinal infections like typhoid, dysentery, cholera, hookworm and the other parasites, all reach a high degree of malignancy in the jungle. Survival must be due only to immunological processes of much greater humoral potency than that common to similar infections in this country, can these high titer antibodies have a primary destructive effect upon the heart and blood vessels? And can the subsequent reactive pathologic changes be responsible for the degenerative changes seen in the cardiovascular system in later life?

Infection has long been recognized as an important contributing factor in the development of these degenerative heart and blood vessel diseases in civilized communities. It is said, however, to have a minor rôle compared to the wear and tear of the psychosomatic factors. Have we now sufficient evidence to attempt a balance sheet? Can we evaluate the relative importance of infection and a way of living and say that in the jungle degenerative cardiovascular disease is the result of *major* infection and *minor* psychosomatics and in civilized communities the equation is reversed to *minor* infection and *major* psychosomatics? Is the problem more than one of academic speculation?

Finally, a word about the acute and more immediate results of the tropical diseases upon the heart. Although rheumatic fever is almost unknown among the Melanesians, valvular heart disease does occur. The aortic valvular mechanism is chiefly involved, this may be the result of syphilis or the syphilis-like jungle infections. Other diseases like malaria, yaws, and tsutsugamushi fever are said to cause heart disorders. I have previously reported the effects of dengue upon the heart.<sup>3</sup> Congestive heart failure following aortic valvular insufficiency is well known to the natives but the common cause of dropsy is chronic coronary heart disease for which, fortunately, the jungle provides an abundance of digitalis-like substances.

### SUMMARY

1 During the early days of the war in the South Pacific, the need for native labor to supplement the work of the Naval Construction Battalions became a necessity. A recruiting unit to select the most desirable Melanesians had, in the course of its program, visited many of the islands of the New Hebrides and Solomons groups. Some of these islands, like Malakula, are perhaps the most primitive unexplored spots left in the world.

2 Since the jungle native is valuable as a member of a labor battalion only in direct proportion to his health, the medical examination of all candidates was of major importance. An unusual opportunity of examining many natives was thus presented, this also included women and children. The latter groups were seen chiefly as a gesture of good will to promote friendly relationships between the natives and the American forces of occupation. Altogether, many hundreds of primitive peoples were seen and many were carefully examined.

3 As a cardiologist, I was particularly interested in various types of heart and blood vessel disease which were discovered. Since many cardiovascular disturbances are said to be the result of modern civilization, an opportunity was given here to evaluate certain well known forms of heart disease in a jungle background. The following observations are thus purely personal, supplemented by opinions expressed by the kindly Native Practitioners and the courteous personnel of the French Colonial Service.

4 Arteriosclerosis and vascular degenerative diseases are common, inhabitants of the jungle age quickly and die in the 40's and 50's.

5 In general, blood pressure levels are not dissimilar to those found in Americans or Europeans of equal age, weight, and sex. However, a small group of Melanesians was discovered with hypertension, most of these were interrelated. High blood pressure in others seemed to be associated with previous renal damage as the result of black water fever and other tropical infections. Hypertensive cerebral accidents are known to the natives.

6 Simple cardiac hypertrophy is common, it was apparently unrelated to any discoverable type of heart disease.

7 Irregularities of the heart were also found. Most of these were sinus tachycardia with high rates. Extrasystolic arrhythmias were the next most common. One case of auricular fibrillation was seen and paroxysmal tachycardia was said to occur.

8 Heart murmurs were discovered. These were classified chiefly as functional systolic pulmonic murmurs. Apical systolic functional murmurs were next in frequency. A group of aortic valvular diastolic murmurs were seen, the etiological background of the pathologic lesions in these caused considerable speculation. Were they due to syphilis or the syphilis-like tropical infections? No presystolic murmurs were found, rheumatic fever is rare among the Melanesians compared to the Polynesians who are the other great racial stock of the South Pacific.

9 The typical syndrome of acute coronary occlusion with pain or angina pectoris is rare, on the other hand, chronic coronary heart disease is common. The latter is the cause of most of the cases with congestive heart failure. The natives have many digitalis-like jungle remedies for the treatment of dropsy and they are familiar with this condition as is shown in their primitive wood-carved ceremonial figures.

10 The absence of the pain pattern in these coronary syndromes led to experiments to determine the pain threshold of the natives compared to negro personnel from a local CB unit, there was no material difference in the two groups. The psychosomatic mechanisms developed by life in civilized communities may be the answer to this important question. The problem merits investigation since it bears directly upon the concept of heart pain.

11 Peripheral vascular disease was also seen, these cases were probably due to the high incidence of arteriosclerosis and atheromatosis and the secondary results of jungle infestations of the feet or a combination of both. Varicose veins and thrombophlebitis are common.

12 Cardiovascular disease appears to be about as frequent among the primitive peoples of the South Pacific islands as among Americans and Europeans. There are some differences, however, in the distribution of the various types of heart and blood vessel conditions but most of the diseases of the cardiovascular system seen in civilized communities are also found in the jungle.

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# THE COMPARATIVE VALUE OF SEVERAL LIVER FUNCTION TESTS<sup>1</sup>

By MYER TEITELBAUM,<sup>†</sup> M D , F A C P , Capt , MC, AUS, *Detroit, Michigan*, ARTHUR C CURTIS, M D , F A C P , and S MILTON GOLDHAMER,<sup>†</sup> M D , F A C P , Major, MC, AUS, *Ann Arbor, Michigan*

THE present dissatisfaction with liver function tests is largely dependent upon a tendency to rely solely upon the result of one particular liver function test, disregarding such factors as the multiple functions of the liver, its regenerative ability or the type of injury. It is obvious that in an organ with multiple functions, such as the liver, the result of a single test may be negative in the face of damage so extensive that it can be ascertained without any laboratory procedures. Such a negative result means only that the test chosen measured a function not as yet altered in that particular diseased liver. The value of any single liver function test, when used, is directly proportional to an appreciation by the user of the function it is testing.

It is highly important to determine whether or not the liver is injured and, if so, the type of injury present. To determine such facts, the limitations of the several liver function tests must be kept in mind so that a proper choice of one or more of them can be made and the results of the tests properly interpreted in the light of physiological or pathological change. If such criteria are used, the results of liver function tests, properly applied and interpreted, often enable one to diagnose impaired liver function early in its course and, at times, to predict correctly the type of lesion present and the general course the disease is following.

Much of our knowledge of the comparative value of liver function tests is based upon the studies of one or two tests done upon a series of patients and a comparison of the results with those of other tests performed upon other patients, by the same, but more often, by different investigators. Though this method of comparison may be entirely accurate, theoretically it lends itself to several sources of error. There may be differences in the personal estimation of the extent and degree of the disease. There may be differences in the classification of liver disease in various clinics with the difficulty incident to the interpretation of one classification in terms of another. There may be minor differences in the technic of performing and interpreting the tests themselves. To avoid these sources of error, we have performed eight different liver function tests at approximately the same time upon each of 153 patients with various types of suspected liver disease. In many of these cases there was neither conclusive clinical nor laboratory evidence of liver disease and hence the results of the liver function tests in the whole

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<sup>†</sup> Contribution to this communication preceded entry into the Army of the United States.

group are not reported at this time. More than 50 of the total number of patients studied presented what we believed to be clinical or proved pathological cases of cirrhosis, neoplasm or hepatitis. The results of liver function tests in these cases can best be dealt with under the headings of the tests.

**Urobilinogen Test** It is now generally accepted that urobilinogen is a pigment formed by the bacterial reduction of bilirubin in the intestinal tract. A large part of the urobilinogen formed is excreted in the stool. Some is absorbed from the intestine and reconverted by the liver into bilirubin. A small amount is excreted in the urine. In the presence of cellular liver disease the amount of unconverted urobilinogen in the blood increases and is excreted by the kidneys. Because of the increased excretion of urobilinogen by the kidneys in some forms of liver diseases, its quantitative estimation in the urine may be of value in determining the presence and extent of cellular liver disease. In using such a test, however, two factors must be kept in mind. In spite of normal hepatic cellular activity there may be an abnormal degree of urobilinogenuria associated with increased blood destruction, the normal liver cannot cope with this demand to convert an abnormally large amount of blood pigment into bilirubin at the usual rate. Furthermore, in chronic renal disease the test is of no value because the kidneys cannot excrete the pigment.

In carrying out this test, we have used a modification of the method described by Wallace and Diamond<sup>1</sup>. Distilled water is added to fresh urine specimens to make dilutions of 1:10, 1:20, 1:40, 1:80, 1:160, etc. To 25 cc of each of these dilutions is added 2 cc of Ehrlich's reagent. A cherry pink color slowly develops which is best seen by looking down through the tube. Readings are made in five minutes. Normally, the appearance of the characteristic color is rarely seen in dilution above 1:20. In this study the presence of this color in any dilution above 1:40 was considered to be abnormal.

In a series of 57 patients with definite liver disease shown in table 1, 43

TABLE I  
Results of the *Urobilinogen Test* in 57 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients with Negative Tests with Direct <i>VdB</i>	Corrected Per Cent Positive
Cirrhosis	41	34	82.9	2	87.2
Neoplasm	6	4	66.7	1	80.0
Hepatitis	10	5	50.0	3	71.4
Total	57	43	75.4	6	84.3

or 75.4 per cent had abnormal excretions of urobilinogen. In the neoplasm and hepatitis groups there were fewer abnormal excretions of urobilinogen than in the cirrhosis group. When the blood bilirubin determina-

tions are compared with the negative urinary urobilinogen tests, it is noted that in the cirrhosis group, two patients had direct van den Bergh reactions. In the neoplasm group, one patient had a direct van den Bergh reaction. When parenchymatous disease of the liver becomes so extensive that obstructive jaundice occurs, bilirubin does not appear in the gastrointestinal tract and the urobilinogen test is of no value as an index of liver disease.

In the absence of an obstructive jaundice and in cases where other causes of urobilinogenuria can be ruled out, the presence of urobilinogen in the urine in dilutions greater than 1:40 is significant. The test is easily and rapidly performed and may help in making a diagnosis of liver disease. Because the test is roughly quantitative it also has value in determining the progress of liver injury.

*Van den Bergh Reaction* The presence or absence of a hyperbilirubinemia is always important in liver disease, and the quantitative van den Bergh reaction is probably the most commonly used single liver function test. Pathologically, a hyperbilirubinemia means either an obstruction of the bile ducts, an inability of the parenchymal liver cells to excrete all of the bile brought to them, or production of bile pigment from blood destruction, greater than the liver can excrete.

Van den Bergh and Muller<sup>2</sup> showed that in obstructive jaundice the characteristic color occurred promptly upon the addition of the diazo reagent to the blood serum whereas in hemolytic jaundice the color appeared only after alcohol was added. These reactions were thereafter called direct and indirect. Later Feigl and Querner<sup>3</sup> noted that some sera developed color upon the addition of the diazo reagent and the intensity of the color increased as the mixture was allowed to stand. The importance of the direct and indirect reactions cannot be overemphasized in the interpretation of the van den Bergh test. Barron<sup>4</sup> has shown that bilirubin, which has passed through the epithelial cells of the liver and is regurgitated into the blood stream, will give a "direct" reaction. In this state it is free bile and is readily excreted by the kidneys. Bilirubin which has not passed through the liver cells gives an "indirect" reaction because, as Barron has shown, it is adsorbed by the serum proteins. In this state it is not readily excreted by the kidneys. The biphasic or "delayed direct" reaction then indicates both free and protein-adsorbed bilirubin in the blood stream and suggests both obstruction of the large bile ducts or small intrahepatic channels and reduced cellular activity of the liver.

The quantitative van den Bergh reaction is of greater value in determining the amount of jaundice than it is in estimating the presence and severity of liver disease. Frequently an extensive impairment in liver function may exist without jaundice and likewise severe jaundice may exist without liver damage. Soffer has emphasized the value of the van den Bergh reaction in following the course of liver disease by showing that in the early stages an indirect reaction is present which later may become biphasic and then direct.



as the lesion progresses Improvement may be indicated by a direct reaction becoming biphasic and then indirect

Table 2 shows that in 58 cases of cirrhosis, neoplasm and hepatitis, the van den Bergh reaction was positive\* in 30 or 51.7 per cent There were 21 direct, no indirect, and nine delayed direct or biphasic reactions Approximately 48 per cent of the cases of known liver disease had normal van den Bergh reactions

**Galactose Tolerance Test** Galactose has been chosen as a substance to measure the carbohydrate function of the liver because there is no renal threshold for its excretion, the endocrine glands have no effect on its metabolism, and it is not utilized by tissues other than the liver

The test is simply and quickly done by the method described by Shay, Schloss, and Rhodis<sup>5</sup> After a 12-hour fast a specimen of urine is collected and tested for sugar Forty grams of powdered galactose are given orally

TABLE II  
Results of the *Van den Bergh Reaction* in 58 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Type of Reaction		
				Direct	Indirect	Biphasic
Cirrhosis	41	17	41.5	12	0	5
Neoplasm	6	4	66.7	2	0	2
Hepatitis	11	9	81.8	7	0	2
Total	58	30	51.7	21	0	9

and urine specimens collected at hourly intervals for five hours No food is ingested during this period, but water may be taken freely The five urine samples are then pooled and the amount of sugar determined by the quantitative Benedict method From this is calculated the quantity of galactose excreted in the urine A total elimination of three grams or more of galactose is an indication of hepatic disease

This test is least satisfactory in determining whether or not liver disease exists Its main value seems to be in the differentiation of a diffuse cellular intrahepatic lesion from other types in which disease is due to an extrinsic obstruction or when considerable regeneration has taken place In patients with considerable jaundice, the galactose tolerance test may prove valuable *early* in the disease When jaundice is due to hepatitis, a positive test is proof of cellular damage When the test is negative early in the disease, it may be of no significance Later in the course of such a jaundice, the test is often of less value because regeneration of liver cells occurs so rapidly that the test may be negative Once a test is positive, however, it offers distinct aid in following the course of the cellular injury

\* In our series indirect van den Bergh determinations of over 7 mg. per 1,000 cc (0.7 per cent) and those showing direct or biphasic reactions were considered abnormal

Table 3 illustrates our results with the galactose tolerance test. Although this is not a large group, it shows that when a diffuse hepatitis is present the galactose test is more likely to be positive than when cirrhosis or neoplasm is present. In cirrhosis, the test is more apt to be negative because the process is not acute, regeneration of the liver structure is constantly occurring, and diffuse cellular disease is a late occurrence. In neoplasm much of the liver is apt to be uninvolved and may function normally. Our experience with the test shows that it is not a good test to determine the presence or absence of liver disease. It is more likely to be positive in diffuse cellular disease (hepatitis) with jaundice than in other forms of intrinsic liver disease, but it will be noted that only approximately 25 per cent of the patients with jaundice had positive galactose tests and nearly one-half of the positive galactose tests were in patients who were not jaundiced at the time the tests were done. Jaundice is an indication for the test.

TABLE III

Results of the *Galactose Tolerance Test* in 54 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients Jaundiced	Number Positive	Number Positive in Patients Not Jaundiced
Cirrhosis	38	7	18.4	15	4	3
Neoplasm	6	1	16.7	2	0	1
Hepatitis	10	3	30.0	8	2	1
Total	54	11	20.4	25	6	5

but the time at which the test is done during the period of jaundice is more important, and a negative test does not necessarily exclude liver injury. Likewise, the test may be positive, in the absence of jaundice.

*Glucose Tolerance Test* Because one of the major functions of the liver is the conversion of glucose to glycogen and its storage, hepatic disease may in some instances produce a disturbance in its metabolism.

Chloroform or phosphorus poisoning or partial hepatectomy in animals produces an atypical blood sugar response. After the removal of 75 per cent of the liver, the glucose tolerance curve deviated from the normal in two ways: it tended to resemble the diabetic type of curve and the fasting blood sugar was low. It has been observed that with damage to the liver, the storage of glycogen may be considerably impaired and when an excess of carbohydrate is given it accumulates in the blood stream and is excreted by the kidney. The presence of a high blood sugar stimulates the production of insulin and with the increased combustion of glucose in addition to its loss through the kidney, a hypoglycemic reaction may occur during the third, fourth or fifth hour after a high carbohydrate meal. Furthermore, because the glucose tolerance test is a routine laboratory procedure, we have

been interested in its value as an index of liver function and have performed glucose tolerance tests on our patients. The standard method was employed, using 1.75 gm of glucose per kilogram of body weight. Patients manifesting diabetes mellitus in addition to their liver disease have not been included in our series.

Table 4 shows that in 54 patients, the glucose tolerance curves were abnormal in 38 or 70.4 per cent. Eight (14.8 per cent) had spontaneous glycosuria. Twelve (22.2 per cent) had blood sugar determinations of 41 mg or less per 100 cc of blood. Five (9.3 per cent) had one or more spontaneous hypoglycemic attacks. Thirteen (24.1 per cent) had fasting blood sugar determinations of 70 mg or less per 100 cc of blood, seven (12.9 per cent) had fasting blood sugar determinations of 71, 72, or 73 mg per 100 cc of blood, and 25 (46.3 per cent) had either fasting blood sugar determinations of 73 mg or less per 100 cc of blood or blood sugar determinations during the third, fourth or fifth hours of the tolerance test.

TABLE IV

Results of the *Glucose Tolerance Test* in 54 Patients with Known Liver Disease

Disease	No. of Patients	Number Positive	Per Cent Positive
Cirrhosis	38	25	65.8
Neoplasm	6	4	66.7
Hepatitis	10	9	90.0
Total	54	38	70.4

of 41 mg per 100 cc or lower. Seven had both. Twenty-six (48.1 per cent) had either fasting blood sugar determinations of 73 mg or lower per 100 cc of blood or hypoglycemic attacks. Four patients had both. Only fourteen patients (25.9 per cent) had normal glucose tolerance curves, no spontaneous glycosuria, no hypoglycemic attacks, and normal fasting blood sugar determinations.

Inasmuch as the glucose tolerance tests were done on the same patients who also had galactose tolerance tests, we are able to compare the relative value of each test. It appears that if the glucose tolerance test begins with a normal or low fasting blood sugar, elevates during the first or second hours to a level higher than normal and then falls to a hypoglycemic level during the third or fourth hour, it is probably indicative of liver disease. Glycosuria may be present during the test and hypoglycemic reactions may also occur. Not uncommonly both reactions are seen in the same patients. A comparison between the value of the galactose tolerance test and the glucose tolerance test shows that the latter is a much more delicate test of liver disease. The glucose tolerance test shows the same tendency, in a greater degree, to require extensive liver cell disease and as a result is an important test to use in differentiating hepatitis from obstructive jaundice.

*Serum Proteins in Liver Disease* *A Blood Serum Protein Determinations* A reduction of the level of serum proteins has been noted in liver disease by many authors. Though it is generally accepted that the serum proteins are synthesized in the liver, there still is insufficient experimental proof that this is true. It has been shown that when animals were given phosphorus and carbon tetrachloride, a decrease in the serum proteins followed the liver injury. Furthermore, it is known that reduction of the serum proteins may be nutritional in origin and that there is a relationship of the serum protein production to vitamin B<sub>1</sub>.

In considering the level of serum proteins as an index of liver function one must also keep in mind that *hypoproteinemia* is often associated with renal disease and with undernutrition. The serum albumin is most often affected and the serum globulin may be elevated. The albumin-globulin ratio may approach unity or may be reversed. Total protein concentration under 6.5 gm per cent and serum albumin concentration under 4.0 gm per cent were considered abnormal.

Table 5 shows that 48 out of 57 patients (84.2 per cent) had a reduction of the serum albumin level below 4.0 grams. From this table one can infer

TABLE V

Results of the *Serum Protein Determinations* in 57 Patients with Known Liver Disease

Disease	Number of Patients	Number with Albumin Concentration under 4.0 grams per cent	Per Cent Positive	Number with Total Protein under 6.5 grams per cent	Per Cent
Cirrhosis	41	33	80.5	21	51.2
Neoplasm	5	5	100.0	4	80.0
Hepatitis	11	10	90.9	7	63.6
Total	57	48	84.2	32	56.1

that hypoalbuminemia may be a good index of liver disease. It is especially valuable in indicating damage to the liver in neoplasm and cirrhosis, in which the galactose and glucose tolerance tests are of less value. It seems to be a more delicate test than those yet considered and is independent of the presence or absence of jaundice.

*B Takata Ara Test* In 1925<sup>6</sup> Takata<sup>6</sup> and later Takata and Ara<sup>7</sup> noted that when chest fluid from a patient with lobar pneumonia was added to a solution of sodium carbonate, mercuric chloride and acid fuchsin, a precipitate of mercuric oxide occurred. They believed this precipitation was due to the globulin fraction of the exudate. Later Staub<sup>8</sup> suggested the use of this test in cirrhosis of the liver, and since then it has been used extensively as a liver function test. Jezler<sup>9</sup> found that the total serum protein content played no rôle, but that the reaction was dependent upon the globulin content of the fluid. He found it positive in widespread parenchymal liver disease.

Table 6 shows that the test was positive in slightly more than half of the cases (51.8 per cent), but it is not a specific test for cirrhosis, as has been claimed, and it may be negative with known liver disease present. An analysis of the figures of table 6 shows that of 36 patients with albumin-globulin ratios of 1 or under, 22 had positive Takata Ara tests. In 19 patients with albumin-globulin ratios over one, seven had positive Takata Ara tests. In 14 of the 27 tests reported negative, the albumin-globulin ratio was 1.0 or less. Of 15 patients in whom the bromsulphalein showed a 35 per cent retention or less, indicating a mild impairment of liver function, the Takata Ara test was positive in only three cases. In 13 instances in which the van den Bergh reaction was indirect and the bromsulphalein showed more than a 35 per cent retention of the dye, 12 individuals showed a positive Takata Ara test. Our figures compare favorably with those of more recent authors who feel that the Takata Ara test is dependent upon the globulin fraction but the reaction is not necessarily positive when the

TABLE VI  
Results of the *Takata Ara Test* in 56 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients with A/G 1.0 or under	Number Positive	Number of Patients with A/G over 1.0	Number Positive
Cirrhosis	41	20	48.8	26	15	15	5
Neoplasm	6	3	50.0	4	3	1	0
Hepatitis	9	6	66.7	6	4	3	2
Total	56	29	51.8	36	22	19	7

albumin-globulin ratio is reversed. Although most of the positive tests (22 out of 29) showed a reversal of the ratio, 50 per cent of those that showed a negative Takata Ara test also had a reversal of the ratio. In comparing the Takata Ara test with the severity of the hepatic lesion as measured by the bromsulphalein test, it can be seen that the test is positive in the more advanced cases of liver disease, but a positive test does not necessarily imply hepatic damage.

**Bromsulphalein Test** In 1909 Abel and Rowntree<sup>10</sup> showed that when injected into the blood stream, phenoltetrachlorophthalein dye was removed by the liver and excreted almost entirely into the bile ducts. Later Whipple, Mason and Peightal<sup>11</sup> demonstrated that when experimental liver injury was produced in animals, the rate of elimination of this dye was directly proportional to the injury. Rosenthal<sup>12</sup> did some similar experiments and then, after injection of the dye, determined its concentration in the blood stream at varying intervals. He suggested that it might be used as a liver function test. Rosenthal and White<sup>13</sup> later used various other halogen substitutes for the chlorine part of the original dye and also found that sulphonation of

the dye prevented its diffusion into the tissues where, later, it was picked up by the liver. As a result they recommend the use of phenoltetrabromphthaleinsulphonate or bromsulphalein. The difference in the action of the original dye and the sulphonated dye is probably due to the former being a colloid and the latter a crystalloid. The weakness in the use of the dye, however, lies in the fact that it is excreted through the bile passages into the intestinal tract. Any lesion, extrinsic or intrinsic, causing obstruction of the bile passages, will delay the excretion of bromsulphalein. In cases of obstructive jaundice due to neoplasm of the ducts, stone, severe hepatitis where the bile ducts may be closed, advanced cirrhosis or acute yellow atrophy, the results of the bromsulphalein tests are not true indices of liver damage when the quantitative van den Bergh reaction is direct. Any direct or biphasic van den Bergh reaction means obstruction and renders the test valueless.

The test is done as follows. 5 mg of bromsulphalein per kg of body weight are injected intravenously. A sample of venous blood is collected in 30 minutes, centrifuged, and the serum divided into two parts. One part is alkalinized with two drops of 10 per cent NaOH and compared with a set of color samples indicating the per cent of the dye present in the blood at that time. The second sample, acidified with one drop of HCl, is placed behind the standard color tubes to give a similar background in comparing the unknown. In 57 cases of cirrhosis, neoplasm and hepatitis there were 29 with indirect van den Bergh reactions. Twenty-five of the 29 cases, or 86.2 per cent, had bromsulphalein determinations that were considered abnormal. Retention of more than 15 per cent of the drug in 30 minutes was considered abnormal. It will be seen in table 7 that the test is non-

TABLE VII

Results of the *Bromsulphalein Dye Excretion Test* in 57 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive	Number of Patients with Indirect Van den Bergh	Number Positive	Per Cent Positive
Cirrhosis	41	37	90.2	25	21	84.0
Neoplasm	6	6	100.0	2	2	100.0
Hepatitis	10	9	90.0	2	2	100.0
Total	57	52	91.2	29	25	86.2

selective and more delicate than any procedure yet considered for determining liver disease. The results are in agreement with those of other investigators who believe that in the absence of jaundice, the bromsulphalein test is the most valuable test in determining the presence of parenchymatous liver injury. The negative tests in undoubted cases of liver disease, as noted in table 7, are indications that the test is not infallible. If positive, the brom-

sulphalein reaction means some degree of liver injury. If negative, it does not necessarily eliminate the possibility of liver damage.

*Macrocytosis as Index of Liver Disease* Since the work of Castle, it is generally accepted that the substance necessary for the maturation of red blood cells is formed from the interaction of an extrinsic factor (food) with an intrinsic factor present in the stomach. The resulting product is absorbed from the intestine, stored in the liver and utilized when needed. Disturbance of this mechanism at any point will produce a macrocytic anemia.

Wintrobe and Shumacker<sup>14</sup> reported a large series of cases of macrocytic anemia in liver disease and, since their work, many similar observations have been recorded. It has been shown that the liver is the storehouse for the material necessary for the maturation of the red blood cells.

A macrocytic anemia may occur in pernicious anemia, syphilis or cancer of the stomach, gastrectomy, pregnancy, obstruction of the intestine, fish tape worm infestation, celiac disease, gastrocolic fistula, and sprue. If these conditions are ruled out, the presence of a macrocytic anemia may indicate liver disease. In these cases, the anemia is seldom as severe and the variation in the cell sizes may be less marked than in pernicious anemia.

The results of mean corpuscular volume determination on 41 cases of cirrhosis, six cases of neoplasm and 11 cases of hepatitis are shown in table 8.

TABLE VIII  
Results of the Mean Corpuscular Volume Determinations  
in 58 Patients with Known Liver Disease

Disease	Number of Patients	Number Positive	Per Cent Positive
Cirrhosis	41	26	63.4
Neoplasm	6	1	16.6
Hepatitis	11	5	45.5
Total	58	32	55.2

It will be seen that in cirrhosis, where the disease process is quite extensive, the incidence of macrocytosis is greater than in neoplasm of liver where large amounts of the hepatic tissue may be normal. In hepatitis, where the process is often acute, regeneration is apt to be quite rapid, and the incidence of macrocytosis is less frequent than in cirrhosis. The test is quickly done, valuable in various types of liver disease, and quite indicative, when positive, of extensive liver damage when other causes of macrocytosis can be ruled out.

#### DISCUSSION

The relative value of any of the eight liver function tests used in this study, in cirrhosis, neoplasm and hepatitis can be seen in table 9. Inasmuch as all of these tests were done on the same patients at approximately the same

TABLE IX  
Results of All Tests in Known Liver Disease

Disease	Number of Patients	Galactose Tolerance Test	Van den Bergh Reaction	Takata Ara Test	Mean Corpuscular Volume	Glucose Tolerance Test	Urobilinogenuria		Serum Proteins		Bromsulphalein	
							Total	Corrected	Hypo-albuminemia	Hypo-proteinemia	Total	Indirect Van den Bergh
Cirrhosis Neoplasm Hepatitis	41	18.4	41.5	48.8	63.4	65.8	82.9	87.2	80.5	51.2	90.2	84.0
	6	16.7	66.7	50.0	16.6	66.7	66.7	80.0	100.0	80.0	100.0	100.0
	11	30.0	81.8	66.7	45.5	90.0	50.0	71.4	90.9	63.6	90.0	100.0
Totals known liver disease	58	20.4	51.7	51.8	55.2	70.4	75.4	84.3	84.2	56.1	91.2	86.2



time, a comparison of their worth can be made. It can be seen that the galactose tolerance test was positive in only 20.4 per cent of the cases, whereas the van den Bergh reaction showed jaundice in 51.7 per cent and the serum proteins were abnormal in more than 84 per cent. The galactose tolerance test may be valuable in differentiating an extrinsic obstructive jaundice from an intrinsic diffuse cellular hepatitis, but its efficiency in doing so is very low. However, it is to be remembered that the test may be positive in the absence of jaundice. The glucose tolerance test is a far better test to use if such a differentiation is desired, for it was positive in 90.0 per cent of our cases of hepatitis whereas the galactose tolerance test was positive in only 30.0 per cent. The van den Bergh reaction is the most established of all the liver function tests and the most universally used. Unfortunately it loses much of its value in differentiating the various types of liver disease if the other causes of increased blood bilirubin are not kept in mind and if the direct, indirect or biphasic reactions are not determined. Alone, it means only that the patient does or does not have jaundice, and if jaundice is present, whether it is an obstructive jaundice, non-obstructive jaundice or a combination of both. It has some value in prognosis, by the character of its reactions, when several determinations are made. The reaction may be normal with advanced liver disease.

The Takata Ara reaction is non-specific and, although it was positive in only about half of our patients, when positive it meant advanced liver disease. In this regard, the test has merit in allowing a prognosis of the severity of the parenchymatous disease. The determination of the mean corpuscular volume is, probably, not a good test for liver function. It was a poor index of disturbed function in neoplasm and was not as good as other tests in hepatitis. The importance of our determinations seems to lie in the relative frequency of macrocytosis occurring in cirrhosis and emphasizes the fact that, if other common causes of a macrocytic anemia can be ruled out, liver disease should be suspected.

The glucose tolerance test has been little used and much maligned as a liver function test. If the curve is interpreted in the light of the physiological findings reported after destruction or removal of large parts of the liver parenchyma, it seems to have definite value as a liver function test. Its simplicity and general use make it a good test. In our series, it was fourth in importance as an index of disease and either as good as or better than all other tests in hepatitis. It is independent of jaundice and hence has importance when the bromsulphalein or urinary urobilinogen tests are of no value.

The urinary urobilinogen test is seldom used but because it is simply done and is an easily performed office procedure, its relative importance as an index of disturbed liver function should be carefully appraised. It can be roughly quantitative and when positive, has value, at least, in pointing to possible liver disease. If other causes of increased urobilinogen are

absent, a positive test immediately warrants further liver function studies. It is a non-specific test and as such only points to the liver as a probable cause of the disturbed urobilinogen excretion. In the presence of jaundice, the test is worthless. It is a good test to combine with the van den Bergh reaction.

The determination of the serum proteins is now being used to a greater extent as a liver function test. Its non-specific nature, however, gives it the same relative value as the bromsulphalein test. Its apparent independence of jaundice enhances its value. When obstructive jaundice is present, our figures show it to be the most delicate test of all those used. Because so little is known about the origin of the serum proteins and the various conditions that may alter it, the value of their determination in liver disease must await further fundamental work.

The bromsulphalein test is the most sensitive of all the eight liver function tests *in the absence of* obstructive jaundice, although it is not infallible. Its quantitative character makes it particularly valuable in following the course of the liver disease during the period when the patient is free of obstructive jaundice. When obstructive jaundice appears, other tests must be used to determine prognosis.

### CONCLUSION

- 1 In patients who are jaundiced, the best tests to use for the estimation of hepatic function are the serum protein determination (hypoalbuminemia) and the glucose tolerance test. Invariably such patients will have had a van den Bergh test already performed.

In patients who are not jaundiced, it appears that the best tests to use are the bromsulphalein dye excretion test and the urobilinogen test. In these patients the van den Bergh, too, will already have been performed.

In either situation, the other tests may well add further information regarding the degree of impairment of hepatic function.

- 2 The value of any liver function test is directly proportional to an appreciation of the function or functions it is testing.

- 3 No *one* test should be considered *the* test of liver function.

- 4 The proper interpretation of a combination of these tests for specific functions will tell much about hepatic function and the degree of its impairment.

- 5 Repetition of certain of these tests from time to time in the course of the disease will further tell whether the disease in the liver is progressing, retrogressing, or stationary.

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# CLINICAL USE OF NEW TYPES OF MODIFIED PROTAMINE ZINC INSULIN\*

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THE report by MacBryde and Roberts<sup>1</sup> concerning the clinical use of a new type of modified protamine zinc insulin in the treatment of diabetic patients with excellent results moved us to use it in clinical trial in a small number of selected cases

It is well known that for the great majority of diabetics, crystalline zinc insulin if divided in proper doses, or commercial protamine zinc insulin (PZI) with convenient shifts of carbohydrate allotments in the diet, will suffice. There are, however, a certain number of patients that cannot be controlled by this means, especially when they require large doses of PZI. Liberation of insulin from PZI is essentially steady during 24 hours and its effect lasting more than one day does not keep pace with the needs in these cases. PZI lacks elasticity to prevent post-prandial hyperglycemia with consequent glycosuria and nocturnal hypoglycemia with danger and inconvenience of insulin shock. Treatment of these cases with combined use of crystalline and protamine insulins did not easily overcome the difficulties. It has been also well established that PZI has an excess of protamine sufficient to precipitate almost entirely the regular insulin in the types of mixture most commonly used. This precipitation effect is especially marked because the pH of such mixtures is always below the iso-electric point of insulin, usually between 4 and 5.

Thus, it was a great therapeutic advance when both types of insulin could be combined in a relatively stable form with adjusted pH, the rapidly acting component of such a combination being measured by assay of the supernatant fluid, after centrifugation of the mixture<sup>2</sup>. This is the type of insulin modification we have used in 16 cases at the Outpatient Clinic of the Wisconsin General Hospital. Selection of the cases from among those consulting at our Outpatient Department was made, bearing in mind that it is precisely here that a trial of clinical usefulness could be better made, although we realize that control and follow-up studies cannot be as complete as in hospitalized patients. As a matter of fact, in a ward patient the constants are first, diet, second, activity, and third, environmental condition. The only variable is insulin, its type and dose. The first three conditions cannot be kept as constant in an ambulatory patient and perhaps it is more accurate to assume that all the factors are variables, since all these patients are engaged in their normal and constantly changing activities. In all the

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cases the diets used ranged between protein 50 to 70 grams daily, fat 90 to 225 grams daily, and carbohydrates 70 to 150 grams daily. No revision of diet was attempted during the course of this study. The following table shows some pertinent data.

The first 10 cases were using PZI regularly for diabetic control in doses ranging from 35 to 75 units daily with an average of 58 units daily. As they were shifted to modified protamine zinc insulin (MPZI) stated, the average dose decreased to 52 units daily and a better control was obtained, as shown by the blood sugars which were taken usually two hours after the noon meal. Cases 11 and 12 had been treated in another clinic with regular insulin in three divided doses. The MPZI was used to avoid several daily

TABLE I

No	Dose and Type of Previous Insulin Units	MPZ Insulin (T 1716) Units	Blood Sugar 2 Hours After Meal		Reason for Change	Clinical Results
			Pre viously	on MPZI		
	PZI					
1	70	66	234	154	Marked nocturnal reactions	Excellent Few and mild early morning reactions
2	70	40	230	160	Low renal threshold for sugar, frequent nocturnal reactions	Less frequent reactions
3	60	65	326	258	Pre-prandial reactions, post-prandial glycosuria	Better control of post-prandial glycosuria
4	50	35	176	138	Marked nocturnal and pre-prandial reactions	Less frequent and milder reactions
5	70	75	200	117	Instability of control, nocturnal reactions	Still having reactions with faster acting types (T-1842, AP-125)
6	50	52	246	218	Late afternoon reactions	Not good Notes recurrence of diabetic characteristics On AP-125, fast acting type
7	65	45	262	258	Frequent nocturnal and before breakfast reactions	Trial on fast acting types (T-1842, AP-125) not successful Good with MPZI
8	50	60	330	216	Poor control of post-prandial glycosuria	Better control
9	45	35	202	142	Post-prandial glycosuria, slight morning reactions	No glycosuria No reactions
10	75	65	264	222	Frequent pre-prandial and nocturnal reactions	No reactions in one month

TABLE I—*Continued*

No	Dose and Type of Previous Insulin Units	MPZ Insulin (T-1716) Units	Blood Sugar 2 Hours After Meal		Reason for Change	Clinical Results
			Pre viously	on MPZI		
11	Regular 15, 15, 15	50	220	128	To reduce number of daily injections	Excellent Fasting blood sugar 114, P C 110, 128
12	15, 0, 20	40	230	168	Instability of control	Fairly steady blood sugar after meals
13	Mixture 3 1 60	55	266	150	Trouble in mixing insulin, poor p c control	Excellent No reactions
14	1 1 60	40	250	175	Instability Low renal threshold	No reactions Better control of post-prandial hyperglycemia, regardless of glycosuria
15	1 1 60	25	164	?	Glycosuria in day-time, nocturnal reactions	
16	Globin 50	35	214	183	Frequent pre-prandial and nocturnal reactions	No reactions in one month

injections and the control secured was excellent although no marked decrease in dosage was noted in these cases. Cases 13, 14 and 15 were using self-prepared insulin mixed in the same syringe. The shift to MPZI was warranted because of the inconvenience of mixing two different kinds of insulin and the possibility of error that actually occurred in several cases. The doses of MPZI required in these patients were consistently lower.

Case 16 had been treated before with globin insulin and complained of frequent late afternoon reactions. The change to MPZI was followed by absence of reaction during a month period although the dosage required was much less.

Several other mixtures of faster acting type were tried. These were completely soluble, containing less protamine. They did not prove satisfactory for the types of patient we have studied. The modified protamine zinc having the 3 1 proportionate effect seemed to meet the requirements of most of our moderate to severe diabetics, as predicted and found by MacBryde and Roberts<sup>1</sup>. This was shown by better post-prandial and nocturnal control of glycemia and consequently of glycosuria, and freedom from frequent hypoglycemic reactions. This modified protamine zinc insulin seems to be unit for unit more effective than the other types of insulin, since smaller dosage brings equal or better control. At present we are trying a completely

soluble mixture, containing slightly less protamine than MPZI. Some of the above described patients are finding it as satisfactory as MPZI, whereas in a few its action is a bit too rapid.

### SUMMARY

Observations on 16 diabetic patients with long-standing and essentially stable disease convince us that the special modified protamine zinc insulin of MacBryde and Roberts is the best type of protamine insulin for most diabetics who require 40 or more units daily. One patient (No. 6) found the modified insulin relatively inactive and was unwilling to make a further trial since beginning acidosis occurred. This experience was not duplicated on any other occasion. One other patient (not tabulated) felt that an extemporaneous mixture (5:3) was superior to the specially modified insulin. In all other cases the treatment with a single daily injection of MPZ insulin was preferable to any other routine tried.

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We are grateful to Dr. F. B. Peck of the Eli Lilly & Co. Laboratory for generous supplies of specially modified insulin (coded as T-1716) and for other combinations of protamine and crystalline insulin, as well as globin insulin.

# ABDOMINAL MANIFESTATIONS OF RHEUMATIC FEVER. DESCRIPTION OF A RIGHT RECTUS SYNDROME\*

By NORMAN REITMAN, M D, *New Brunswick, New Jersey*

THE abdominal manifestations of rheumatic fever have been known since Andral, in 1839, called attention to the presence of abdominal pain in cases showing other evidences of rheumatic fever. The French, who were the first to study this problem, found signs and symptoms of peritoneal irritation in rheumatic fever, manifested chiefly by attacks of abdominal pain at the onset of rheumatic activity, and found that when the arthritic pains began the abdominal pains stopped and vice versa.

This important association of abdominal pain and rheumatic fever has largely escaped the attention of the internist and the surgeon. Poynton,<sup>1</sup> in 1925, was the first to describe a chronic peritonitis in a fatal case of rheumatic fever with most of the exudate around the liver and spleen. A loud peritoneal friction rub had been heard during life. Poynton felt that no fatal case of rheumatic fever ever had acute rheumatic changes in the appendix. Paul,<sup>2</sup> in 1930, described the autopsy findings in a rheumatic with polyarthritides, pericarditis, pleurisy, endocarditis and pain in the abdomen. This patient was found to have a serofibrinous peritonitis, very similar to the pleural and pericardial lesions, with underlying Aschoff bodies in the liver and spleen. Worms, in 1930, treated two cases of peritoneal syndrome in rheumatic fever with salicylates and found that the pain and physical signs subsided rapidly.

Although attention has been called to the peritoneal reactions in rheumatic fever, no definite work has pointed to the rectus abdominis muscle as the source of the abdominal pain. Within the past few years several cases of abdominal pain were studied by the author who found that the apparent cause was a rectus myositis which appeared as a manifestation of rheumatic activity. Wood and Ehason<sup>3</sup> in a most comprehensive review of this subject were the first to suggest that the abdominal pain might be due to rheumatic abdominal myositis. These authors, in reporting a case of rheumatic peritonitis, in 1931, stated that the cause of the abdominal pain might be due to (1) rheumatic involvement of the abdominal muscles analogous to torticollis, lumbago or "growing pains," (2) abdominal lymphadenitis or inflammation of the lymphoid tissue in the appendix, (3) pain referred from the pleura, pericardium, diaphragm or spine. However, Wood and Ehason, in the final analysis, felt that rheumatic fever produces a true peritonitis. This feeling was based upon the elicitation of a peritoneal friction rub in two cases,

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This work was done before the author entered the Military Service.



the finding of subperitoneal edema in two cases at operation and the post mortem observation of peritonitis in fatal cases of rheumatic fever reported by Paul and Poynton

In the cases reported below it was felt that the pathologic lesion was localized to the right rectus muscle rather than an intra-abdominal source. The reason why the right rectus muscle was involved rather than both sides is not clear, unless it be due to the fact that people with pain in the right side of the abdomen are more likely to consult a physician because of the well known location of pain in appendicitis.

#### CASE REPORTS

*Case 1* Mrs B K, a 50 year old housewife, was seen in November 1939, in consultation with Dr S Z Neiman. The patient had been ill for 24 hours with abdominal pain and fever. There was no nausea or vomiting. The patient had had chorea in childhood but there was no history of rheumatic heart disease.

Examination revealed marked spasticity in the right lower quadrant with moderate tenderness over McBurney's point. There was no rebound tenderness. The heart was of normal size. The first apical sound was roughened and impure. In the left lateral recumbent position a definite, presystolic, rumbling murmur of mitral stenosis was heard. The temperature was 101° F, pulse 104, respirations 25, and blood pressure 140 mm Hg systolic and 82 mm diastolic.

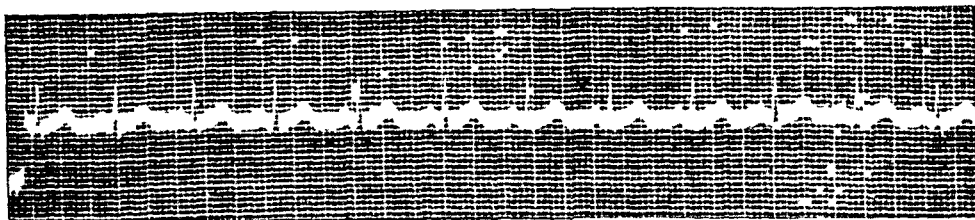
In view of the finding of rheumatic heart disease the sedimentation rate was determined and found to be 50 mm per hour (Westergren). The white blood cell count was 13,500, polymorphonuclears 72 per cent, lymphocytes 28 per cent. The patient was put on salicylates with a prompt cessation of her pain and temperature in 12 hours. The sedimentation rate remained elevated for three weeks during which time the patient was asymptomatic. This patient subsequently developed auricular fibrillation and moderate congestive heart failure. Her sedimentation rate was not elevated after the original attack. There was no return of abdominal pain.

*Case 2* Mrs L H, a 21 year old secretary, was first seen in November 1941, because of sharp, sticking, abdominal pain of 24 hours' duration. Pain originated in the right lower quadrant and radiated to the right thigh. No nausea or vomiting was experienced. The patient stated that she had had one or two similar attacks previously.

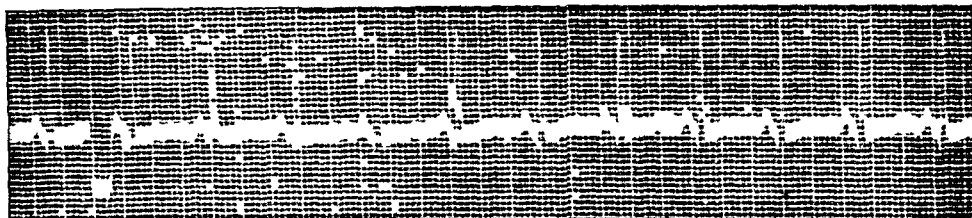
Examination revealed definite tenderness over McBurney's point with marked spasticity in the right lower quadrant. No rebound tenderness was elicited. The white blood cell count was 10,500, polymorphonuclears 63 per cent, lymphocytes 28 per cent, eosinophiles 2 per cent, mononuclears 7 per cent. Nothing else was found on examination. Because of the equivocal blood count the patient was treated conservatively and the symptoms abated in three days. It is interesting to note that the only medication given was aspirin-phenacetin-caffeine capsules for the relief of pain.

In March 1942 the patient returned with a similar episode of right lower quadrant pain, tenderness over McBurney's point, no rebound tenderness, nausea or vomiting. The patient had definite tenderness on rectal examination. On splinting the abdomen tenderness was still present. The temperature was 100.2° F, pulse 96, respirations 22. The white blood cell count was 12,900, polymorphonuclears 70 per cent, lymphocytes 25 per cent, mononuclears 5 per cent. Because of the tenderness on rectal examination it was felt that a laparotomy was indicated. At operation an appendix was removed showing no gross or microscopic evidence of disease.

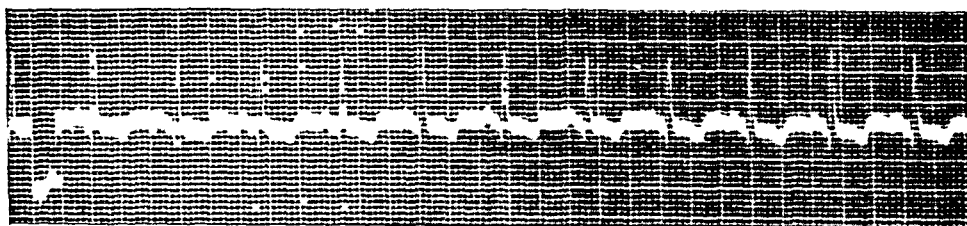
Postoperatively the patient ran a stormy course with fever between 101° and 103° F and tachycardia. On the third postoperative day she developed a maculopapular eruption on the extensor surfaces of her arms and legs, characteristic of erythema nodosum. The white blood cell count rose to 15,000 with 82 per cent polymorphonuclears and 18 per cent lymphocytes. The abdominal wound was healing well. On the sixth postoperative day the sedimentation rate was found to be



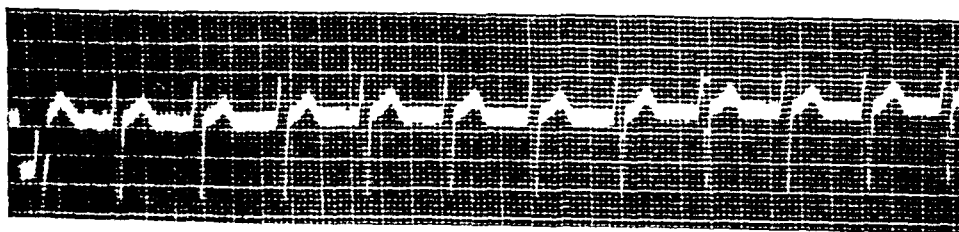
LEAD I



LEAD II



LEAD III

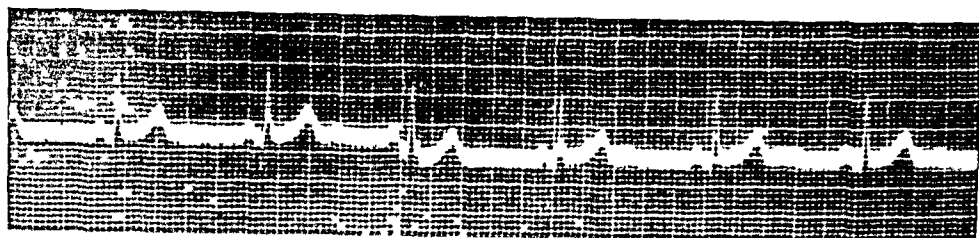


LEAD IV

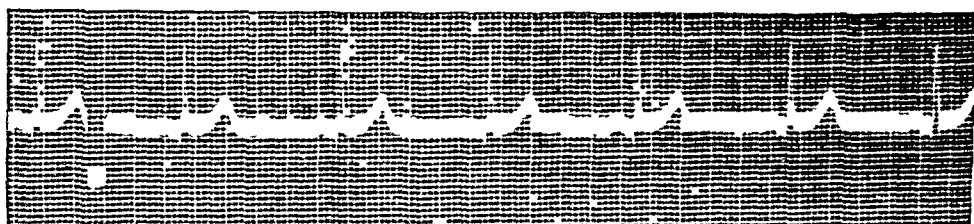
FIG 1 Case 2, April 26, 1942

110 mm per hour (Westergren). In view of this finding the possibility of acute rheumatic fever with abdominal manifestations was considered and the patient was put on salicylates. Within 24 hours her temperature returned to normal and the pain had disappeared. Tachycardia remained and an electrocardiogram taken at this time revealed inversion of the T-waves in Leads II and III (figure 1), indicating some degree of myocardial change or damage.

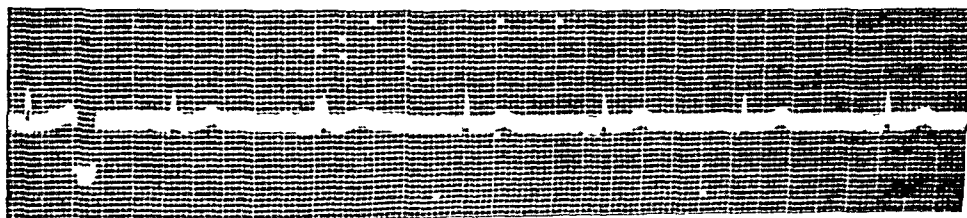
The sedimentation rate remained elevated and the erythema nodosum was present for about three weeks. At this time the patient was symptom-free, had a normal pulse, and another electrocardiogram revealed a return of the T-waves in Leads II and III to the normal, upright position (figure 2)



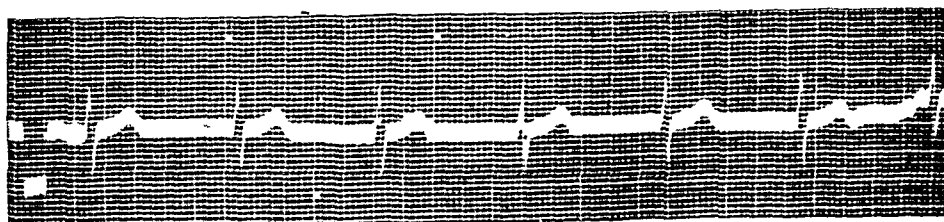
LEAD I



LEAD II



LEAD III



LEAD IV

FIG 2 Case 2, May 11, 1942

The patient had a mild return of rheumatic activity with right lower quadrant pain about two months later. Following bed rest and salicylates, her sedimentation rate returned to normal within three weeks. Since then this patient has remained well and no further evidence of rheumatic heart disease has developed.

*Case 3* Miss I S, a 15 year old school girl, was seen in May 1942, complaining of pain in the right side of three days' duration, which was sharp, constant, localized

to the right lower quadrant, and aggravated by walking. The patient was subject to frequent colds and sore throats but had had no known manifestations of rheumatic fever.

On examination the temperature was 99.8° F, pulse 110, respirations 20, blood pressure 114 mm Hg systolic and 64 mm diastolic. The abdomen was markedly tender on palpation in the right lower quadrant with the point of maximal tenderness over McBurney's point. No rebound tenderness was found. There was marked spasticity of the muscle in the right lower quadrant. On splinting the abdomen by sitting up without use of her hands, the tenderness remained, thereby localizing the process in the superficial muscles of the abdominal wall.

The heart was found to be enlarged to the left. There were low, rumbling presystolic and loud systolic murmurs at the mitral area, a soft systolic and a loud blowing diastolic murmur was heard at the aortic area. A presystolic thrill could be felt at the cardiac apex but none was present at the base. On fluoroscopy the patient had marked enlargement of the left auricle and left ventricle. Although the patient had definite evidence of mitral stenosis and insufficiency and aortic insufficiency with definite cardiac enlargement, there was no history of diminished cardiac reserve and this was the patient's first knowledge of her damaged heart.

In view of the previous experience the sedimentation rate was determined and found to be 38 mm per hour (Westergren). The white blood cell count was 15,200, polymorphonuclears 76 per cent, lymphocytes 20 per cent, eosinophiles 4 per cent. There was no shift to the left in the Schilling index. The patient was placed on salicylates with immediate subsidence of the abdominal symptoms. The next day her abdomen was soft and there was only slight generalized abdominal pain. The day following, the patient developed some mild migratory joint pains involving the wrists, ankles and knees, which subsided after three days. Sedimentation rate remained elevated for three and one-half weeks before returning to normal.

The patient's subsequent course was poor as she remained a recurrent and chronic active case of rheumatic fever, developing heart failure, auricular fibrillation and ran a low febrile course for many months, finally dying in March 1944, from congestive heart failure. An autopsy failed to reveal any evidence of peritoneal thickening or appendiceal disease. The patient had cardiac hypertrophy, dilatation of the left ventricle, left auricle, right ventricle, mitral stenosis and insufficiency and aortic insufficiency. Numerous pulmonary infarcts were also found.

**Case 4** Miss J. J., an 18 year old colored maid servant, was seen in April 1942, in consultation at the St. Peter's General Hospital, New Brunswick, New Jersey, because of abdominal pain. In this patient the onset of abdominal pain occurred about one week prior to examination. She was seen in the surgical clinic where some right lower quadrant tenderness was elicited. A gastrointestinal series was performed and a report of "a pathological appendix due to non-filling" was made and the patient was admitted for appendectomy.

At the time of the examination a further history was obtained of a severe tonsillitis six weeks prior to admission and the onset of a dull precordial ache with some dyspnea on exertion within the past two weeks. On examination the temperature was 100.4° F, pulse 116, respirations 22, blood pressure 124 mm Hg systolic and 66 mm diastolic. The abdomen was definitely tender over McBurney's point but no rebound tenderness was present. There was definite spasticity of the muscles in the right lower quadrant and on splinting the abdomen, as described above, the tenderness persisted. The heart was not enlarged but there was a soft blowing diastolic murmur over the aortic area transmitted to the mitral area. No other murmurs were heard. The blood Wassermann reaction was negative. A diagnosis of rheumatic heart disease with aortic insufficiency was made and the possibility of abdominal myositis due to rheumatic fever was again considered. The sedimentation

rate was 66 mm per hour (Westergren) The electrocardiogram revealed a P-R interval of 0.24 second The white blood cell count was 13,300, polymorphonuclears 72 per cent, lymphocytes 22 per cent, mononuclears 6 per cent, eosinophiles 2 per cent

On salicylates the patient's pain promptly disappeared and within two weeks the P-R interval diminished to 0.14 second The sedimentation rate remained elevated for six weeks before returning to normal This patient was followed for one and one-half years and has had no recurrence of rheumatic fever or signs of cardiac decompensation, although the aortic insufficiency has remained

### DISCUSSION

These four cases all presented the difficult differential problem of appendicitis and the question of operation was considered in each One of the patients (Case 2) had such clearcut signs, including tenderness on rectal examination, that operation was essential However, all these cases presented signs atypical enough to make one doubt appendicitis and consider other causes for the clinical picture

In all cases there was an absence of initial cramp-like, generalized abdominal pain, followed by nausea and vomiting, as seen in the majority of cases of acute appendicitis The initial complaint was severe pain, localized from onset to the right lower quadrant There was some nausea in Case 2, but no vomiting in any The discovery of spasticity and marked tenderness over McBurney's point, without rebound tenderness, is the most significant finding on examination If this symptom were due to appendiceal disease, one would expect a soft abdomen and tenderness early in the course and definite rebound tenderness when the peritoneum became involved and muscle rigidity had developed These cases were all characterized by the absence of rebound tenderness Another clinical feature of importance was the persistence of tenderness when the muscle tension of the rectus abdominis muscle was increased by having the patient raise the neck or attempt to sit up without the use of the hands In all cases the tenderness persisted when this maneuver was performed If the signs were due to an intra-abdominal pathologic lesion this protective splinting of the intra-abdominal organs would cause a disappearance of the tenderness Therefore, it is believed that the signs and symptoms were due to an acute rheumatic myositis of the muscles of the abdominal wall rather than to an intra-abdominal lesion

Another outstanding feature differentiating these cases from appendicitis was the relief of symptoms and signs upon the administration of salicylates in therapeutic doses This persisted even though low grade fever and other manifestations of a general reaction continued

The elevated sedimentation rate was the important differential laboratory procedure In appendicitis a normal sedimentation rate is present unless suppuration with gangrene has occurred Such a patient is usually sicker than our patients appeared to be The white blood cell count is also of help In acute appendicitis one usually finds a leukocytosis with a polynucleosis

and a shift to the left. In our cases of rheumatic abdominal myositis there was a mild leukocytosis but the differential count remained normal.

The evidence of rheumatic fever elsewhere in the body—heart, skin, joints, etc.—in the presence of atypical signs of appendicitis, should always make one wary. Geptill,<sup>4</sup> in discussing the differential diagnosis of the abdominal manifestations of rheumatic fever from acute appendicitis, shares the same opinion. He found eight cases of pseudoappendiceal syndrome in 160 cases of rheumatic fever. He also noted the relative absence of vomiting in abdominal rheumatic fever and its presence in 90 per cent of the cases of appendicitis. Rectal tenderness, which was present in Case 2 of our group and was one of the deciding factors in favor of surgery, also occurred in a few of Geptill's cases, the cause of which is unexplained. He also noted the absence of a shift to the left in the Schilling index. A preceding history of sore throat was found in 30 to 40 per cent of the rheumatic cases and was absent in appendicitis.

In general when a young patient with a previous rheumatic history or signs of rheumatic valvular damage presents himself because of abdominal pain, which is in the right lower quadrant, without any nausea or vomiting, having right rectus spasm with tenderness over McBurney's point, no rebound tenderness, and running a moderate fever, one must seriously consider an abdominal form of rheumatic fever, most likely due to myositis of the rectus abdominis muscle. This possibility should be further substantiated by an elevated sedimentation rate, leukocytosis with a normal Schilling count and rapid subsidence of the abdominal picture under salicylate therapy even when the general reaction continues. The presence of a preceding diarrhea and alternation of abdominal and joint phenomena are striking findings reported among the cases in the literature.

Recently Babbage, McLaughlin and Frum,<sup>5</sup> of the U. S. Navy Medical Corps, have reported a series of 141 cases of right rectus muscle strain with a clinical picture suggesting acute appendicitis. These cases occurred in healthy navy recruits undergoing their basic training, where they were subjected to severe physical exercise. They note the localization of pain immediately to the right lower quadrant over the rectus muscle and find that the tenderness and pain are aggravated by increasing the muscle tension by raising the head and shoulders from the bed without the aid of the arms. Marked spasm of the rectus muscle was also noted. These findings, definitely due to local disease in the rectus muscle, are identical to observations made by the author, thereby suggesting the superficial origin of the signs and symptoms in the cases reported above.

Babbage, McLaughlin and Frum used procaine injection of the rectus muscle as a differential diagnostic test in doubtful cases, finding an elimination of pain and spasm in a rectus strain and no effect in appendicitis. This suggests the possible use of this procedure in cases of abdominal rheumatic fever with rectus abdominis myositis and will be tried in future cases.

## SUMMARY AND CONCLUSIONS

1 Four cases of abdominal pain as a manifestation of acute rheumatic fever have been presented. From the observations made, it seems that the origin of the pain is a myositis of the rectus abdominis muscle.

2 The outstanding features are sudden onset of sharp pain in the right lower quadrant without radiation, no nausea or vomiting, marked muscle spasm with tenderness over McBurney's point and absence of rebound tenderness.

3 When such symptoms and signs are found in a patient with a previous rheumatic history the possibility of rheumatic rectus abdominis myositis must be considered.

4 An elevated sedimentation rate and a leukocytosis with a normal Schilling index is a further evidence of the rheumatic origin of the symptoms.

5 A therapeutic test with salicylates will cause subsidence within 12 to 24 hours even though other manifestations of rheumatic fever persist.

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# ANOREXIA NERVOSA: THE DIAGNOSIS AND TREATMENT OF INANITION RESULTING FROM FUNCTIONAL DISORDERS \*

By JOHN M BERKMAN, M D , *Rochester, Minnesota*

IT is interesting that Gull, who first recognized anorexia nervosa as being a condition resulting from starvation, should have also discovered the cause of myxedema, a disease which bears his name. He has been appraised by the English as being one of the most brilliant clinicians of all times. His diagnostic acumen, ability of keen observation and unquestioned curiosity must have been enviable, particularly at a time when laboratory assistance and other aids to diagnosis were far inferior to those which we have at our disposal at the present time. The study of anorexia nervosa has in certain respects been much like the study of myxedema. Both conditions are in most instances completely reversible. Unmistakable physiologic changes occur during the development as well as during the recovery in each instance and in spite of these extensive changes in physiologic processes, significant laboratory findings, with the exception of a low basal metabolic rate common to both, are few. What we know about these conditions has been learned almost entirely from observation, careful inquiry into the medical history and an active sense of curiosity.

In 1930 the writer <sup>1</sup> presented an analysis of a series of cases of anorexia nervosa in which the patients had been seen at the Mayo Clinic from 1917 to 1930 inclusive. The following report is based on additional experience with patients with anorexia nervosa who have been observed at the clinic since that time.

## SYMPTOMS AND DIAGNOSIS

The symptoms and findings in any one case of marked inanition as a result of starvation from functional disturbances are good examples of those of any other case in this group. Consequently, the clinical picture constitutes a clinical entity as satisfactorily as any other clinical entity with which we may be considerably more familiar. Anorexia nervosa occurs in young men, however, in such comparative infrequency that for reasons of facility in presentation they are not specifically referred to in this paper.

Clinically the degree of functional anorexia or vomiting extends from instances in which these symptoms are so mild as to have no further unfavorable result than to cause the person to maintain his weight considerably below his normal weight and appear thin, to instances in which these symptoms are so severe that the starvation results in extensive inanition and cachexia. Consequently, the margin between making a diagnosis of anorexia

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nervosa and making one of underweight or undernourishment is rather wide and depends on the physician making such a diagnosis. No limiting criteria have been established to distinguish between these two degrees of undernourishment. Rather than to use the term "anorexia nervosa" to designate the entire group of patients presenting inanition as a result of functional disorders it might seem advisable to use such terms as "functional anorexia" or "functional vomiting" with inanition, and to qualify the degree of inanition present by giving the percentage of weight loss from the normal.

Inanition secondary to functional disturbances is due to functional vomiting, or functional anorexia, or to a combination of the two, which results in an inadequate caloric intake. The time required for the development of the inanition and the extent to which the inanition may reach depend on the degree of inadequacy of the caloric intake.

In general, patients presenting vomiting alone usually seek medical consultation comparatively early. A diagnosis of functional vomiting is usually made before an appreciable degree of inanition has occurred. However, when vomiting has persisted and is associated with anorexia and a marked degree of inanition, the treatment becomes much more difficult. The vomiting must be overcome before a successful increase of the caloric intake can be brought about. There is no difference in the eventual outcome for the patient who refuses to eat and the patient who does eat but vomits immediately afterward. Patients who vomit an hour or more after meals may do so without vomiting enough food to cause much loss of weight. In such instances weight is lost very slowly and over a long period.

In most of the cases in which marked inanition develops, it does so primarily because of functional anorexia. Although there may be some infrequent vomiting, the vomiting plays only an insignificant rôle in the development of the inanition. As a general rule these patients keep the bulk of their diet below that amount which gives them distress and results in vomiting, consequently, vomiting is not as frequent nor as serious a symptom as anorexia.

I have roughly estimated the daily caloric intake of a number of these patients who had reached a marked degree of inanition and whose weights varied between 55 and 75 pounds (25 and 34 kg) to be between 900 and 1,300 calories. This low body weight had been stationary for some time.

The symptoms of anorexia nervosa may be divided into two groups: the psychic and the somatic. Briefly, the psychic symptoms resemble the emotional reactions of the spoiled child: loss of morale, loss of pride as evidenced by subterfuges, unsound excuses and explanations regarding symptoms, apathy, reticence, paucity of ideas and negativistic tendencies. Patients suffering from anorexia nervosa may be very tiring in conversation, lack spontaneity, and offer only answers to questions, the answers usually being incomplete. They are difficult to reason with and display mental fatigue. In spite of the large number of psychoneurotic complaints, they

do not express concern over their loss of weight or cachectic appearance. They evade a discussion of the true situation. This in general is a description of the psychic symptoms of the group as a whole, however, it pertains particularly to the younger group of patients. Although the older group beginning at about 26 years of age have tendencies toward the same reactions, they may show them to a lesser degree. However, it must be remembered that these reactions are the result of the effect of starvation on the individual's mental make-up. Consequently, the degree of these reactions will vary with the strength of that individual's mental make-up. Infrequently, the strength of personality may be maintained to such a degree that this alone may in certain instances have the tendency to lead one astray in making a correct diagnosis.

The somatic symptoms consist of evidence of marked loss of weight with the appearance of age, pallor without anemia, in some instances hairiness of the arms and legs, dryness of the hair and skin, intolerance to cold with cold hands and feet, low blood pressure and a slow pulse rate. More than half of the female patients suffering from anorexia nervosa give a history of amenorrhea. The finding of an atrophic type of uterus is common, particularly in young nulliparous women when inanition is marked. The patients complain of various indefinite gastrointestinal disturbances, the most consistent being constipation. In spite of unmistakable evidence of dietary incompetence, there is a lack of recognizable avitaminosis. There may be edema of the ankles, which in most instances is slight. Sighing dyspnea is a frequent occurrence. No particular evidence of caries of the teeth described elsewhere has been observed in patients seen in the clinic. The symptoms and findings of inanition or anorexia nervosa could be more aptly referred to as the depressant effects of starvation.

As to the classification of these patients in regard to age one might logically assume that the condition might occur in more or less equal proportions at all ages. However, clinically this is not the case and I believe that there are logical and sound psychologic reasons why this does not happen. Although the direction of reaction as a result of starvation at all ages is much the same, yet these reactions are tempered and varied in degree by the effects of age.

Functional anorexia and functional vomiting are very common occurrences following psychic disturbances among children up to the age of 12 to 14 years. As a general rule, however, certain temporary situations responsible for the nervous disturbance are corrected long before any marked demonstrable physical changes as a result of starvation have appeared. The mental immaturity, susceptibility to suggestion and trusting tendencies of children make the treatment of anorexia and vomiting due to functional disorders much more approachable than the treatment of the same condition among patients of 14 and 15 years of age and older. Consequently,

it is a very rare occurrence for a child \* to go on to a condition of marked inanition and cachexia as a result of starvation due to functional anorexia or vomiting

During puberty and thereafter, however, the formation of individual ideas and the feeling of independence make the situation much more difficult to handle. Few parents have escaped at least in some degree the worries and problems associated with the battle of adolescence. At these ages romance, the excitable effects of menstruation and the feeling of independence are at a high level. Their desire for recognition of this independence makes this group particularly susceptible to resentment of parental advice and curtailment of their need to assume the privileges of adult life. The magnitude of these desires is common knowledge. Consequently, the adolescent group is surrounded by factors which make them particularly susceptible to psychic disturbances and their ability to make mountains out of mole hills may explain why they are capable of carrying those factors responsible for marked inanition and cachexia to such extremes. In the great majority of cases of anorexia nervosa, while the peak of the weight loss and the full blown picture of inanition may occur several years later, the condition has its origin during puberty or during the few adolescent years following. A small group may have the occurrence of the psychic upset during the third decade, however, as the decade progresses the comparative frequency of cases becomes progressively less.

In the adolescent group the basis for the psychic upset is frequently found to be in the parent. This does not necessarily mean, however, that the parent is dominating or unreasonable, but depends on the degree of the child's resentment to regimentation and the degree of insistence on the part of the parent. The parent is not necessarily responsible for the psychic upset, as the disturbing factor may originate in school, a teacher or in disappointments far removed from the parents and home life. Nevertheless, in this age group there is invariably a psychic upset present although the psychic upset itself or the degree of its effect may not be admitted or in some instances possibly not appreciated by the patient himself.

There is a subgroup of the group of adolescents which I believe deserves brief mention. This subgroup consists of young girls, 13 to 15 years of age, who during the grade school years are somewhat overweight. When they reach the first year of high school they may realize that they are overweight or they may be cruelly reminded of this fact by others. As a result they markedly cut down on their food intake so as to reach the desirable appearance as quickly as possible. However, when they have become satisfied with the amount of weight lost they find that it is impossible for them to eat the amount sufficient to maintain their weight at the level desired. Conse-

\* When anorexia nervosa associated with marked inanition occurs before the age of 10 years and persists continuously through adolescence and the years of completion of growth, definite evidence of retardation of skeletal development as well as of development of sexual characteristics occurs

quently, loss of weight continues to progress to a point at which the symptoms so typical of inanition appear. In this instance then the anorexia, inability to partake of a normal caloric intake in three meals a day and vomiting follow rather than precede the development of inanition. Further remarks will be made in regard to this.

The group of patients more than 30 years of age comprise a much smaller portion of the entire group than those less than 30. The condition of the younger members of this group may be identical with that of those patients under the age of 30 and be secondary to a definite psychic upset. However, after 30 years of age the frequency of the condition decreases and the clinical picture becomes less and less characteristic. In general, the inanition does not have the tendency to reach marked degrees of cachexia and these patients frequently pass unnoticed except for the fact that they are considerably underweight. The older the patient, the less chance one has in assisting him to return to his normal weight. This probably is due to the presence of fixed ideas and inability to cooperate. The older the patient, the more attention one must give to exclusion of organic disease. There is one group of patients in which the sequence of events follows much the same course as that seen in the younger group. This includes older patients who after the extraction of all teeth either have faulty dentures or do not use dentures.

In many of the cases in which a diagnosis of anorexia nervosa was made at the clinic, diagnoses of disturbances of various glands of internal secretion had been made previously and the patients had been treated with injections of glandular preparations without results. Because of the complexity of the clinical syndrome associated with inanition resulting from functional starvation there is little difficulty in understanding why one who is not familiar with this clinical picture tends to attribute its origin to a disturbance of the glands of internal secretion. In other cases diagnoses of vitamin deficiencies had been made and the patients had been treated with intravenously administered vitamins as well as vitamins by mouth. In still other cases diagnoses of Simmonds' cachexia or of other diseases which had been suggested by the presence of the amenorrhea had been made.

In some instances anorexia nervosa had been suspected but this diagnosis had been discarded because the patient was felt not to respond favorably to an increase of food intake. It must be remembered that a daily caloric intake well above the calculated daily caloric requirement for that particular patient must be maintained for several months before the patient regains his normal weight. This probably does not occur in most instances until the end of a six month period. Also it should be kept in mind that in certain instances during an increased caloric intake there may at first be a satisfactory initial gain of weight which may occur for a week or even 10 days and be followed by another week or 10 days during which time little or no weight is gained. However, after this period the patient, without any increase of caloric intake, will begin to gain again. The initial gain of

weight may be explained by an early retention of electrolytes and water. During the period in which no gain of weight occurs, the excretion of water may be balanced roughly by an actual storage of flesh, which may be fat or muscle or both. From that time on, a constant gain of weight occurs. I believe that this period during which no gain of weight occurs has been responsible for the lack of faith in a diagnosis of anorexia nervosa in a number of instances.

I do not believe that Simmonds' disease or other diseases of the pituitary gland need to be considered very often in the differential diagnosis although by others this has been considered a necessity. I am assuming that the term "Simmonds' cachexia" designates a condition of marked inanition and cachexia secondary to atrophy or a destructive lesion of the anterior lobe of the pituitary gland. In this connection it is important to bear in mind that, as Sheehan and Murdoch<sup>2</sup> have pointed out, cases of severe degrees of pituitary necrosis often are not characterized by cachexia. In the experience of the clinic inanition associated with anterior pituitary insufficiency regardless of the cause is the exception rather than the rule. In my experience it is much more important in certain instances to exclude regional and terminal jejuno-ileitis, as a number of patients suffering from this condition have lacked some of the characteristic symptoms of that disease and their symptoms have closely simulated those of anorexia nervosa.

The value of laboratory tests in assisting one to make the diagnosis is limited. There is a lowered rate of metabolism, the degree depending on the length of time the inanition has existed, the degree of the inanition and the normal rate of metabolism of the individual prior to the onset of the inanition. There is a tendency to a depression of the values of the gastric acids, a finding of low blood sugar and a flat glucose tolerance curve. In some cases low values for urinary 17-ketosteroids have been encountered. Normal diuresis after ingestion of water in the "water test" for Addison's disease often does not occur. Assays of the urine for gonadotropic substance (prolan) show that it is either greatly reduced or absent and, as one might expect, the urinary content of estrogenic material is likewise reduced or absent.

### TREATMENT

In the treatment of anorexia nervosa there are three factors which should be considered to be of primary importance: namely, discussion of the situation with the patient, the bulk of the diet and its caloric content.

A frank explanation of the cause of the inanition, an outline of the treatment to be carried out and the reason why the treatment is to be carried out in the manner to be described should be given to the patient before the treatment is begun. The patient should be reassured that in spite of her aversion to food and the discomfort associated with it the treatment will not cause her any great discomfort. It should be pointed out, however, that it is to be expected that she will experience some distress and a sensation of

fullness after meals, both of which before long will gradually become less. It should be explained, also, that this postprandial distress will be only a temporary discomfort but necessary for her to tolerate before reaching a point at which her daily caloric intake will be sufficient to allow her to overcome the condition of inanition. Sufficient time should be given for this discussion so that the patient understands the situation and agrees to co-operate willingly. It is important that these patients receive the minimal degree of sympathy but it is of equal importance that they be not antagonized. If the patient is accompanied by a parent or relative, it is well to have the companion present at the discussion. I have made it a point to see these patients every day for a period of a week or 10 days or until the patient has developed enough confidence to overcome the aversion to food which previously had been the dominating factor militating against her recovery. In the discussion it must be constantly kept in mind that emotional reactions of hysterical type are the primary factors to be overcome in the treatment of anorexia nervosa.

It may be well at this point to digress and point out another factor in the production of some of the symptoms which these patients exhibit. After anorexia or vomiting has existed for a time sufficiently long for signs of inanition to develop, symptoms occur which I believe are entirely secondary to the anorexia and vomiting and do not relate to the inanition per se. By this time in the development of the inanition the patient often experiences epigastric distress and a sensation of overdistention after eating small amounts. The appetite is satisfied and the distress eventually occurs after only a few tablespoonfuls of food. These symptoms persist and as time goes on less and less bulk is tolerated. Finally an actual fear of as well as an aversion to food develops. It seems likely that these symptoms are due to a functional sensory disturbance associated with the stomach itself and are the result of continued lack of bulk in the diet which has been a necessary accompaniment of the period of starvation. If the normal daily moderate distention of the stomach at mealtime plays a rôle in the maintenance of normal psychosomatic appreciation of the food in the stomach, then in anorexia nervosa, because of a continued lack of bulk in the diet, an absence of this mealtime distention of the stomach may well result in an increase of the appreciation of the presence of food in the stomach. As this progresses, even small amounts of food in the stomach may impart a definite and unpleasant sensation of fullness.

An analogous situation is seen in the disturbance of the urinary bladder known as "habit frequency" in which patients cannot tolerate the normal degree of bladder distention. In general, patients will tolerate distention of the urinary bladder to a volume of 300 cc without symptoms. Patients, however, who have practiced habit frequency will not tolerate that amount and some of these will tolerate less than half of that amount without experiencing distressing symptoms of vesical distention. Irritability of the urinary bladder in patients having habit frequency is gradually overcome

following an explanation of the situation and advice to decrease the frequency with which the patient voids in spite of the urgency. Rarely, however, it becomes necessary to perform hydrostatic dilatation of the bladder with the patient under anesthesia. For the most part these symptoms of irritability brought on by habit frequency may be analogous to a like effect occurring in the stomach as a result of a continuous absence of bulk in the diet. It seems possible that the alteration of the psychosomatic appreciation of volume occurring in the urinary bladder as a result of habit frequency could similarly occur in the stomach, giving rise to a distressing sensation of distention following the ingestion of small amounts of fluids and solids. The response which occurs in patients suffering from anorexia nervosa to a method of treatment which fundamentally is the same as that given in habit frequency strongly supports this hypothesis.

Vomiting in cases of anorexia nervosa can be regarded as a conditioned reflex, the active stimulus being a sense of fullness which apparently with development occurs at a lower and lower threshold and appears when less and less bulk is present in the stomach. The reversal of this habit is similar to the reversal of the habit frequency of the urinary bladder.

In such an organ as the stomach, which has the properties of contraction and relaxation, I know of no method of measuring volumes for purposes of comparison except in the presence of such conditions as marked dilatation of the stomach due to obstruction at the outlet. For a number of years roentgenologic examinations have been performed on patients suffering from anorexia nervosa, particular attention having been given to the motor function of the stomach, but little of value has been forthcoming from these observations.

Prior to 1938, it had been our custom to serve these patients a high protein diet which consisted of a daily caloric intake of 3,000 calories. At that time an attempt was made to keep the bulk of the diet as low as possible. In some instances, and after the lapse of a period of several months or longer, the results were good. However, in other instances, the patients soon became discouraged because of the associated distress and sensation of fullness. Inability to eat less than half the amount served was very discouraging and as a result, in a number of instances, subterfuges of various kinds were practiced to avoid that distress. To a number of these patients this manner of treatment seemed impossible and they refused to continue with it. Others, however, were able to tolerate the distress and after some time found that they were able to eat everything served to them with a gradual lessening of the distress. This group in general went on to complete recovery. At that time a number of patients whose inanition and anorexia were marked, particularly if vomiting was present, were hospitalized and fairly frequently the treatment was begun by nasal tube feeding. At the present time, however, in spite of marked inanition and anorexia as well as vomiting, it is rarely necessary to hospitalize these patients for nasal tube feeding.

In 1938, we began to treat these patients with particular attention to the

amount of bulk in the diet. Although the caloric value of a high protein diet does not reflect accurately the amount of bulk in the diet, nevertheless, progressively increasing a high protein diet by addition of 300 calories will gradually increase the bulk of the diet. Keeping this in mind, these patients have been treated with the purpose of bringing about a gradually increasing distention of the stomach at mealtime. The treatment has been carried out in the following manner. A rough estimate of the patient's daily caloric intake prior to her arrival at the clinic is made. To this amount is added 300 calories. The patient is served a high protein, high vitamin diet based on that number of calories (usually from 1,300 to 1,500 calories) and is asked to eat everything served to her. For the first few days the patient may complain of distress and a sensation of fullness. However, after several days these symptoms gradually become less. After five or six days the caloric content of the diet is increased by another 300 calories. For the first two or three days discomfort is again experienced, however, the symptoms again become less. This procedure is repeated until the caloric intake is approximately 3,400 or 3,600 calories. These patients experience far less distress eating this diet than they experienced eating the initial diet based on 1,300 to 1,500 calories. Frequently, the distress becomes markedly decreased before the diet based on 3,200 calories has been reached. In a number of instances, the diet has been increased to one based on 3,800 calories or more without difficulty.

At the time of dismissal the patient is instructed in the diet by a dietitian. She is advised to weigh herself two or three times a week. She also is advised that if her gain is not progressive, she can feel sure that without realizing it she has gradually decreased her diet. Because of this tendency I feel it necessary to increase the caloric intake to 3,400 calories or more. The patient is told what her normal weight should be and is advised to continue her diet until her weight reaches a point 5 pounds (2 kg) greater than her normal weight. Since using this method of treatment the results have been very satisfactory and a number of patients who previously might have been felt to have a unfavorable prognosis have responded surprisingly well and have overcome the inanition.

Orange juice as well as small doses of insulin given 20 minutes before meals for the purpose of stimulating the appetite has been felt by us to be ineffectual and consequently neither has been used as a part of the treatment for a number of years. Also the use of desiccated thyroid as an adjunctive measure was discontinued in 1939. If desiccated thyroid is given in doses sufficient to elevate the basal metabolic rate, this decreases the initial gain of weight. Psychologically, in these cases an initial gain of weight is important.

It appears worth while to report the case of a patient who was recently seen in the clinic and whose difficulties apparently had to do with the problem just presented.



## CASE REPORT

A woman 33 years of age came to the clinic on January 26, 1944. She gave a history of having had an eye infection in 1939, which had been diagnosed as being secondary to a general infection. Her weight had been 180 pounds (82 kg) and her height was 5 feet 6 inches (168 cm). She had lost her appetite and subsequently had found it impossible to eat more than half of each meal served to her. As a result, during the subsequent two years, her weight had decreased from 180 pounds (82 kg) to 110 pounds (50 kg). However, during the summer of 1941, by voluntary forced feedings of more than three meals a day and in spite of postprandial vomiting which had occurred every day or two, she had increased her weight to 140 pounds (64 kg).

At that time she had experienced an attack of fairly severe epigastric pain associated with vomiting which had been present for part of one day. She had entered a hospital and a complete investigation of the gastrointestinal tract had been made with negative results. She remained in the hospital for a period of 10 weeks, during which time vomiting had occurred frequently as a result of epigastric pain, distress and a sensation of distention which occurred during and after her meals. She had been nervously upset and complained of insomnia and exhaustion. A diagnosis of neurosis was made. After leaving the hospital, during which time her symptoms had persisted, she found her weight to be 102 pounds (46 kg).

In an attempt to regain her lost weight she began to have six to eight small meals a day consisting of foods primarily of high caloric value. After having followed this procedure for several months she found that her weight had increased to 140 pounds (64 kg) and that she was feeling very well. However, she also observed that when she tried to restrict her food intake to three meals a day it was impossible for her to maintain her weight. Eating more than a small amount at each meal brought on her old distress and sensation of fullness.

Following examination she was found to be in good physical condition. Roentgenograms of the gall-bladder showed it to be normally functioning and roentgenographic studies of the stomach and colon gave negative results. The results of other laboratory investigations were either negative or within normal limits.

The dietary treatment previously described was carried out. The initial caloric value of the diet was 1,400 calories. The bulk associated with the diet at first caused some distress, which after several days became less. The diet was increased in the manner previously mentioned to 2,600 calories. Because of an increase of weight, the caloric value of the diet was decreased to 2,000 calories, where it was maintained. However, the bulk of the diet was progressively increased. The patient was dismissed from our care on February 17, 1944. At that time she was eating everything served to her and experienced only minor distress and very little discomfort from the sensation of fullness.

*Comment* The patient whose case has just been reported is the only one that we have had an opportunity to observe who had regained her normal weight by frequent feedings rather than the customary three meals a day. The recovery from the inanition without overcoming postprandial symptoms is what one would expect as a result of frequent feedings and points out the effect of continued lack of bulk in the diet.

## RESPONSES TO TREATMENT

Several different responses common to the group as a whole occurring during treatment have been observed and appear to be worthy of mention. During the first part of treatment breakfast is by far the most difficult

meal with which these patients have to contend. Patients who have dogged resolution to get well may be able to eat the first three meals without unexpected discomfort but have difficulty in eating on the following day. Occasionally, the fourth and fifth meals will result in failure while the following three meals may again not be too difficult. Through persistence on the part of the patient, however, a decrease of the degree, or in some instances disappearance, of postprandial symptoms may occur rather early in the treatment.

Observations made on patients suffering from marked inanition under treatment who have done unusually well from the beginning have within the first two weeks shown unmistakable signs of improvement as evidenced by lessening of postprandial distress, noticeable color to the skin of the face, improvement of attitude, increase of strength and a sensation of warmth. Whether these changes are on the basis of increased food intake or on a psychic basis is difficult to say. However, the sensation of warmth which replaces the constant intolerance to cold, occurs long before elevation of the basal metabolic rate begins and can hardly be completely attributed to the specific dynamic action of protein. The constipation, which in most instances is better described as obstipation, is frequently replaced in a short time by regular bowel movements.

Most patients suffering from marked inanition who respond favorably to treatment will, if closely observed, show edema of the feet and ankles at the end of the first week or 10 days. The edema may not be noticed unless particularly looked for. However, patients who do exceptionally well may have marked edema of the feet and ankles to such extent that they cannot wear shoes. This occurs as a rule during the first two weeks of treatment and concomitantly with the initial gain of weight. The serum protein levels are found to be within normal limits and examinations of the urine as well as tests of renal function give normal results. This edema probably is best explained by the early retention of electrolytes and water which has previously been discussed. As a general rule the edema lasts for a week or two, however, in some instances it lasts longer. Reassurance and general measures usually employed in instances of static edema are advised. It appears that the degree of edema which occurs is in direct proportion to the rapidity of the successive increases of the caloric intake which the patient will tolerate.

The basal metabolic rate is elevated gradually without the administration of desiccated thyroid and appears to return to normal concomitantly with the return of the patient to a normal weight. In one instance the return of the basal metabolic rate followed the return of the patient to normal weight whereas in another the return of the basal metabolic rate preceded the return of the patient to a normal weight.

The function of menstruation is frequently affected in women who have anorexia nervosa. It has been previously mentioned that more than half of the women have amenorrhea. When menstruation persists, although it

may occur with regularity, the amount of flow is diminished. It is well known that a psychic or nervous upset can produce periods of amenorrhea. Inasmuch as this factor has been observed fairly frequently in these cases, this etiologic element must be considered and the fact that amenorrhea or menstrual irregularity fairly frequently antedates loss of weight strongly suggests this. In the patient who has undergone marked loss of weight as a result of inadequate food intake a physiologic reason certainly exists for an inadequate production of gonadotropic principle by the anterior lobe of the hypophysis and for inadequate response on the part of the ovary. Estimations of the amounts of gonadotropic principle in the urine of patients suffering from marked inanition reveal negative results. In cases in which a dietary insufficiency has not existed sufficiently long to bring about marked inanition, there may be evidence of this material in the urine. Examination of the pelves of these women yields results that are rather in proportion to the duration of the amenorrhea. If this has been present for some months, as it fairly frequently is, the mucosa of the vagina is atrophic and vaginal smears reveal a constant state of deficiency of estrogen. Likewise, the uterus will be found to be in various stages of atrophy owing to the long continued and complete lack of stimulation from the ovary. Atrophy of the breasts occurs, although the loss of weight no doubt plays a part in the reduction of their size. In any event, the picture, in so far as the genital tract is concerned, is one of inactivity and atrophy.

The time of onset of the amenorrhea varies greatly. As mentioned previously, amenorrhea may be the first symptom. In other instances it may coincide with the onset of loss of weight, while in still others the inanition may be severe before amenorrhea occurs. In a few cases menstruation may persist in the presence of marked inanition. Perhaps the patient's selection of food has something to do with this. It is conceivable that the woman whose diet contains a relatively large amount of protein might preserve menstrual function longer than one whose chief intake is carbohydrate. However, this occurrence of dietary selection has not been particularly observed by us. When amenorrhea occurs in these patients, the picture becomes one of failure of the pituitary gland to secrete gonadotropins, a failure which is probably due to starvation. The psychic effect in some instances may have helped to initiate the condition but in all probability has little to do with its persistence.

The attitude toward treatment of the amenorrhea in these patients is of importance. Perhaps one could better say that the attitude toward the condition of the genital tract of these women is important. The majority of these patients are young and their reproductive functions are of primary importance to their future. This fact has usually been recognized prior to their coming to the clinic and because of the obvious inactivity of the anterior lobe of the pituitary gland many of them have received injections of extrinsic gonadotropins, without benefit in most instances as one might expect. The presence of a lowered rate of metabolism has been recognized

in most instances and thyroid has been administered previously without beneficial effect on the menstrual function

It must be kept in mind that most of these women or girls have previously been healthy and have experienced menstrual function within the limits of normality and amenorrhea has developed only as the condition of inanition developed. In other words, there had been no previous evidence of malfunction of the glands of internal secretion concerned with the function of menstruation. Evidence of malfunction did not develop until those glands were deprived of a normal internal environment. Consequently, it has seemed that a return to normal nutrition and so to a normal environment for the pituitary, ovary, thyroid and uterus was the logical first step in treatment. As has been indicated previously, the rate of metabolism rises to within normal limits as the patient, as a result of normal food intake, returns to her normal weight. In many instances the menstrual function returns to normal under the same circumstances and without specific treatment. To some patients who are seen after many months of inanition associated with amenorrhea estrogens have been administered cyclically three weeks out of four in doses of 0.5 mg of diethylstilbestrol by mouth. This has been done to aid in priming the uterus for subsequent return of ovarian function and to shorten the period of marked atrophy often seen in these cases. In a few cases amenorrhea persists after the return of normal weight and nutrition. When this is true, the estrogens are administered cyclically for the foregoing reason and to imitate the rise and fall of levels of estrogen in the body which may act as a stimulation to the production of gonadotropins. In other cases under the same circumstances low voltage roentgen stimulation to the pituitary and ovaries has initiated menstrual function. Extrinsic gonadotropins may be given a trial under similar circumstances.

In conclusion, it might be suggested that in the care of the type of patient just discussed a consideration of starvation as a cause of the condition be not eliminated as too elementary and discarded for a diagnosis more complex, less understandable and far less hopeful.

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# ELECTROCONVULSIVE SHOCK THERAPY AND CARDIOVASCULAR DISEASE\*

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THE deliberate induction of convulsions in the presence of known or suspected cardiovascular disease would seem to be a very hazardous undertaking. However, it has been possible to treat a considerable number of such patients for psychiatric disorders with very little trouble and a low mortality rate. When the convulsion is induced by the application of an electric current to the brain, there is no direct trauma to the cardiovascular system, and one would expect no more trouble than would follow one or two minutes of strenuous exercise. The results in this series of cases would seem to bear this out.

The following study concerns a group of 750 cases treated with electroconvulsive shock therapy at Mercyville Sanitarium. Among this group were 38 cases with known cardiovascular disease. Most of the patients had mental depressions. The psychiatric results did not differ greatly from those reported in numerous papers on the subject. They were in general very good.

In the group were 19 cases with presumptive to positive evidence of coronary artery disease. Five of the cases had definite histories of previous coronary occlusions together with T-wave negativity in Leads I, II or IV of the electrocardiogram. One patient, a woman aged 74, had a complete left bundle branch block. Two patients had prolongations of the PR intervals to 0.24 second and 0.25 second, respectively. The other patients had definite inversions of the T-waves in Leads I, II or IV. All of these patients withstood the electroshock therapy with no untoward manifestations noted.

Five patients who had auricular fibrillation were treated during the presence of this abnormality. One of these patients was a woman aged 51 at the time her treatments were started. She had had known rheumatic heart disease for many years. There had been two previous episodes of decompensation. The patient had a marked involutional psychosis and she was decompensated for the third time on admission to the sanitarium. There was very marked ascites and dependent edema. The patient was digitalized, acidified with potassium nitrate, and given repeated injections of salyrgan. She was very restless and uncooperative and little progress was made in the attempt to establish compensation. The patient's general physical and mental condition seemed to be getting worse, so in desperation electroshock therapy was started. After a few treatments, the patient became more composed and cooperative and her edema lessened. By the time the patient had had eight treatments she was very much better mentally. However, she

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did not maintain the gain, but again became depressed, negativistic and uncooperative. She was given five more treatments with again an improvement which did not last. She then received treatments intermittently for several months. The patient had a total of 56 convulsions between April 7, 1942 and July 16, 1943. During all of this time the patient also received salyrgan intermittently and her ascites and edema never entirely cleared. However, the patient's mental condition gradually did improve and it was possible to lengthen the interval between treatments. The patient was finally discharged to her home and her physician reported (June 1, 1944) that the patient was now well mentally, but was still receiving her regular salyrgan injections.

The second patient with auricular fibrillation was a woman aged 40 who had rheumatic heart disease and one previous episode of decompensation. She developed decompensation after her tenth treatment. This responded promptly to digitalization and the administration of diuretics and the patient required no further electroshock therapy, as she recovered from her mental disease (schizophrenia-catatonic type).

The third patient with auricular fibrillation was a woman aged 75 with no history of cardiac disease or vascular hypertension. However, she did have generalized arteriosclerosis and moderate cardiac enlargement. She withstood the treatment without incident.

The fourth patient with auricular fibrillation was a woman aged 48 who had had known rheumatic heart disease for several years. Decompensation had not occurred. On January 8, 1943, the patient had had a cerebral embolus with a right hemiplegia. About three months after the vascular accident she had developed a schizophrenic psychosis. On June 24, 1943 she had another embolus which lodged in the left lower leg. Although the patient had marked pain, and temperature and color changes in the foot, collateral circulation was established with the aid of papaverin and an intermittent venous occlusion apparatus. On April 11, 1944, electroshock therapy was instituted. At that time the patient's hemiplegia had improved very little. She had no use of her right hand and was able to use the leg just enough to walk with the support of an attendant. She received a total of 16 electroshock treatments from April 11, 1944 to June 23, 1944. There was no noteworthy change in her physical condition, but mentally she improved and was discharged to her home on July 9, 1944. When last heard from (August, 1944) the patient was in good spirits and adjusting well to her hemiplegia.

The fifth patient with auricular fibrillation was an emaciated woman (height 61¼ inches and weight 62.5 pounds) of 50 years, who had rheumatic heart disease but no episodes of decompensation. She had developed depression, negativism, and aversion to food. She was just about the thinnest person the writer has ever seen. She was fearful and resistive about everything. A diagnosis of probable schizophrenia was made. It seemed ob-

vious that the patient would soon die unless something drastic was done, so she was started on electroshock treatment. By the time she had had four treatments the patient was cheerful, affable and cooperative, and she ate her meals. Two days after the last treatment the patient developed scattered chest râles and a fever of 102° F. She was given sulfamerazine and the temperature became normal, but she continued to have chest pain. Her condition seemed to be good, but seven days after the last treatment the patient suddenly became dyspneic, cyanotic, and in shock, and died in an hour. An electrocardiogram taken a half hour before death showed some increase in the prominence of the S-waves in Lead I, as compared with the pre-treatment record, but it was not definite enough to verify a diagnosis of pulmonary embolism. No autopsy was done, and the exact cause of death remains uncertain.

Treatment was given to nine patients with hypertension, that is, with a systolic blood pressure over 200 mm of mercury. In no case were any complications encountered during the administration of electroshock therapy. One of the patients was a woman aged 56 with hypertension approaching the malignant phase. The blood pressure on admission was 215 mm Hg systolic and 120 mm diastolic. Examination of the ocular fundi revealed marked narrowing of the retinal arteries, many hemorrhages and exudates and slight papilledema. The patient had had a cerebral vascular accident a few months before her admission and there was a coarse tremor and slight hyperreflexia of the right arm. The patient was very depressed, unresponsive and poorly oriented. A provisional diagnosis of psychosis due to cerebral arteriosclerosis was made. The matter was discussed with the patient's husband and a very poor prognosis was given him. However, it was explained to him that the seemingly obvious diagnosis of psychosis due to cerebral arteriosclerosis might be wrong and that the patient might have an independent mental disease, which would respond to convulsive shock therapy. He was anxious that something be done, so with some misgivings the patient was started on shock therapy. She was given a course of eight convulsions. By the time the treatments were finished the patient seemed to be hopelessly confused and unable to answer the most simple questions. However, within three weeks she became oriented, pleasant, cheerful and she recovered good insight. She was discharged recovered from her mental illness on February 14, 1943. Her blood pressure on discharge was 245 mm Hg systolic and 130 mm diastolic. The diagnosis of psychosis due to cerebral arteriosclerosis was revised to involutional psychosis melancholy type. The patient's physician reported (June, 1944) that the patient was living and well mentally, but that her hypertension was the same.

Three other patients with previous cerebral vascular accidents were treated with electroshock therapy with no untoward results.

One patient, a woman aged 44 with rheumatic heart disease without decompensation, was treated. She had a harsh presystolic murmur, some cardiac enlargement, and an inverted T-wave in the fourth lead of her

electrocardiogram She was given 15 electroconvulsive shock treatments with no complications and no noteworthy change in her mental condition (chronic schizophrenia)

### COMPLICATIONS

The only complication other than the one death and the development of decompensation mentioned above was the development of auricular fibrillation, which occurred in one case This patient was a woman aged 70, whose electrocardiogram was normal and who showed no evidence of cardiac disease other than generalized arteriosclerosis before the treatments This patient developed auricular fibrillation after 12 treatments She returned for further electroshock therapy after 11 months At that time the auricular fibrillation had ceased, and it did not recur with the administration of 10 more electroshock treatments

### CONCLUSIONS

Electroshock therapy can be given with remarkably little danger in cases of serious organic disease of the cardiovascular system In a series of 750 patients treated with electroshock therapy, there were 38 cases with positive evidence of previous damage to the cardiovascular system With one exception all of these patients survived the electroshock treatment with remarkably few ill effects and complications Nearly all of the cases treated were suffering from severe mental illnesses, which might well have terminated fatally from undernutrition or suicide if shock treatment had not been used



# PRESENT STATUS OF CHEMOTHERAPY IN TUBERCULOSIS

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THE enthusiasm for chemotherapy of clinical tuberculosis which has been expressed by some authors of articles in newspapers and popular magazines is not as yet shared by most physicians who are utilizing these preparations, although it is widely felt that steady progress is being maintained. Premature dissemination of unreliable information to patients and their relatives can do serious harm if it serves to discourage acceptance of effective conventional treatment, including sanatorium care and collapse therapy. It appears presently important to provide in one article, in a widely circulated medical journal, up-to-date, authentic information on chemotherapy of tuberculosis. With one exception,<sup>1</sup> recent articles for medical readers have appeared in journals intended for specialists or in foreign medical journals.

In 1932 Wells<sup>2</sup> summarized the accumulated knowledge of chemotherapy in tuberculosis and was led to the conclusion that none of the many remedies proposed had demonstrated ability to arrest the progress of this disease in man or in experimental animals. He concluded with these prophetic words: "Probably some new success with some other bacterial infection will be needed to stimulate a new attack on the more difficult problem offered by tuberculosis."

## EXPERIMENTAL INVESTIGATIONS

The impetus which Wells thought was needed was provided by the discovery of the chemotherapeutic efficacy of sulfonamide compounds against a variety of bacterial infections. Rich and Follis<sup>3</sup> first recorded the fact that sulfanilamide possessed limited but definite ability to retard the rate of development of experimental tuberculosis in guinea pigs. Soon thereafter observations were extended to include sulfapyridine<sup>4</sup> and azosulfamide (prontosil)<sup>5</sup>.

The results suggested that other new chemotherapeutic substances should be tested against experimental tuberculosis as they became available. Promin (sodium p,p'-diaminodiphenylsulfone-N,N'-dixetrose sulfonate) had been supplied to us early in 1940 by Dr. E. A. Sharp† for clinical trial in pneumococcus and streptococcus infections of the respiratory tract of man and this drug was the first of the sulfone series to be tried against tuberculosis of experimentally infected guinea pigs. The preliminary results<sup>6</sup> were much

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more encouraging than any previously observed with sulfonamides and led to a long series of investigations. It was shown<sup>7</sup> that promin was capable of actually arresting the progress of otherwise uniformly fatal tuberculosis in guinea pigs and that such results could be achieved even when treatment was delayed for six weeks after inoculation. In a subsequent crucial experiment,<sup>8</sup> laparotomy and biopsy of the liver were performed before treatment, permitting actual comparison of the same lesions before and after administration of the drug. This procedure appeared to provide proof that true retrogression, resolution and even apparent healing of lesions resulted after several months of continuous treatment.

It was logical that other sulfone derivatives be synthesized and subjected to similar experiments to determine their therapeutic efficacy against tuberculosis experimentally induced in guinea pigs. A moderate number of such substances has been produced and tested<sup>9, 10, 11</sup> but full reports have been made only on those which have showed promise. Among such promising compounds were disodium formaldehyde sulfoxylate, diaminodiphenylsulfone<sup>12, 13</sup> (diasone) and 4,2'-diaminophenyl-5'-thiazolesulfone (promizole)<sup>14</sup>.

The experimental observations of the effects of the drugs mentioned in preceding paragraphs have been verified and amplified by several laboratories<sup>12, 15, 16, 17</sup>. It may be concluded, therefore, that several drugs of the sulfone series are effective in combating and arresting experimentally induced visceral tuberculosis of guinea pigs. The recorded results indicate (1) that life of animals which continue to receive treatment can be prolonged indefinitely, (2) that grossly visible lesions of tuberculosis diminish in size or disappear from the viscera of treated animals and (3) that on histologic examination evidence of healing trends can be observed, including fibrosis, encapsulation and occasionally calcification. These findings are in striking contrast to the progressive, destructive, fatal disease of untreated control animals. It is important to note that tubercle bacilli usually were not completely eradicated and that latent disease remained even after extremely prolonged treatment, being rekindled into activity when treatment was suspended<sup>15, 18</sup>. In this important respect all available chemotherapeutic agents fall distinctly short of the ideal, even in experimental studies.

### CLINICAL INVESTIGATIONS

*Promin*. Prompt application of experimental findings to the problems of clinical tuberculosis was attempted. In March, 1941 the first volunteer patients received sulfone therapy for pulmonary tuberculosis at the Mineral Springs Sanatorium. It was soon discovered that human beings did not tolerate promin as readily as did guinea pigs and that only a third to a half of patients could comfortably and safely tolerate doses by mouth which were adequate to yield significant concentrations of the drug in the blood. In May 1942, we reported<sup>19</sup> preliminary clinical results before the National

Tuberculosis Association, meeting in Philadelphia. These results were encouraging but by no means convincing, and the studies were not adequately controlled to justify conclusions being drawn. The original series of 36 treated patients was the subject of a second progress report<sup>20</sup> which was likewise only cautiously optimistic. Other investigators<sup>21, 22, 23</sup> noted similar effects and usually left the impression that a safe and practicable chemotherapeutic remedy for tuberculosis had not been developed. Zucker, Pinner and Hyman<sup>24</sup> could detect no therapeutic effect of promin when it was utilized clinically. However, it should be noted that these workers administered the drug intravenously. When given by this route, the drug is metabolized differently than when given orally.

*Diasone* An apparent exception to the view that safe, practicable chemotherapy for tuberculosis is still to be sought is expressed in the report of Petter and Prenzlau<sup>25</sup> concerning the clinical application of disodium formaldehyde sulfoxylate diaminodiphenylsulfone (diasone), but no convincing therapeutic effect was observed by one of us (Pfuetze),<sup>26</sup> who used diasone for 15 months under conditions similar to those of Petter and Prenzlau. The appearance of subsequent clinical reports concerning treatment with diasone will be awaited with unusual interest and we propose that judgment concerning the efficacy of diasone be withheld until these are available.

*Promizole* Of the effective drugs, promizole first appeared to have unusual clinical interest because of its low toxicity for man<sup>27</sup>. Clinical studies now in progress already indicate that promizole falls distinctly short of the ideal remedy. We already have concluded that it has no dramatic effect comparable to that observed following treatment of acute diseases with sulfonamides.

One patient with renal tuberculosis has taken this drug in large doses for 10 months continuously without tubercle bacilli being eradicated from the urine. Nine other similar patients have taken promizole for renal tuberculosis for shorter periods of time, often with some apparent symptomatic benefit, but without eradication of the bacilli in a single instance. Treatment of these patients is being continued because of palliative effects and with the hope that cumulative benefits may be observed.

Five patients with tuberculous meningitis have received promizole without therapeutic benefit. In the case of meningitis reported by Keith,<sup>28</sup> in which the patient recovered following treatment with promizole, the presence of tuberculosis never was proved and in his report Keith wrote "It should, however, be pointed out that acceptable proof of a tuberculous infection by the production of the disease in an animal inoculated with spinal fluid from the patient was not established. The evidence of tuberculosis, while clinically convincing, therefore, must be considered merely presumptive."

Two patients with proved military tuberculosis have received promizole under our direction. One of these patients received 24 gm of promizole daily for 16 days. In neither case was there any beneficial effect.

More encouraging results have been obtained in treatment of other forms of extrapulmonary tuberculosis (cutaneous tuberculosis and tuberculid, tuberculous lymphadenitis, tuberculous sinuses, etc.) but conclusions are not warranted at this time.

A controlled study of promizole therapy in pulmonary tuberculosis is now under way with other collaborators, following a scheme previously outlined,<sup>29</sup> but significant results may not be known until more time has elapsed.

In the majority of cases in which promizole is taken in large doses (12 to 16 gm per day) moderate to severe anorexia and upper abdominal distress develop, especially after three or four weeks of such treatment. If the dose in such cases is reduced to 8 to 10 gm per day, the distress usually is obviated. Administration by mouth of such dietary supplements as yeast tablets and preparations of liver extract has appeared to ameliorate the gastrointestinal symptoms. Patients with defective renal function, such as frequently accompanies advanced renal tuberculosis, excrete the drug slowly and hence require restriction of dosage and careful, individualized management. No evidence of renal damage produced by promizole has been observed. Adverse effects on the blood rarely are noted except when huge doses are administered (up to 24 gm per day). In a few cases acquired allergic sensitivity to promizole has developed 10 to 20 days after institution of treatment and toxic erythema has appeared but promptly has faded following cessation of the treatment.

We have encountered no toxic manifestations of critical severity in observation of more than 85 patients treated, approximately 75 per cent of these have received prolonged treatment (30 to 300 days). This is in striking contrast to the toxic effects observed with other sulfone drugs. The lack of toxicity appears to be due, at least in part, to the fact that the drug is conjugated in the human body, forming a soluble compound which is readily excreted. Concentrations of the drug in the blood are usually rather low (1 to 3 mg per 100 cc). In a few instances, higher concentrations (5 to 12 mg per 100 cc) have been achieved as a result either of excessive dosage or of defective renal function. In such cases considerable malaise developed which might be attributed to the drug.

It has been reported previously<sup>14, 30</sup> that promizole produces consistently a diffuse parenchymatous hyperplasia of the thyroid glands of guinea pigs and rats. This goitrogenic effect appears to be similar to that of derivatives of thiourea, sulfocyanates, and some other goitrogenic agents. This effect is reversible on discontinuation of administration of the drug. These facts were available to us from the beginning of our clinical observations and hence particular effort has been made to determine if any goitrogenic effect would be exerted on patients who received promizole. Palpation of the thyroid gland, determination of the basal metabolic rate and determination of values for blood cholesterol have shown no physiologic derangement following prolonged administration of this compound.

In the case mentioned in a previous paragraph, in which the patient received 24 gm of promizole daily for 16 days for treatment of military tuberculosis, no hyperplastic changes were found in the thyroid gland at necropsy. On the basis of observations of animals, it would appear that the amount of promizole which this patient received should have been adequate to produce definite hyperplasia of the thyroid gland in susceptible animals.

### THE NEED FOR CAREFUL RESEARCH IN TUBERCULOSIS

Clinical studies designed to appraise the therapeutic value of substances for treatment of tuberculosis should be carried out with the same controlled scientific methods which are universally demanded in laboratory studies. In no disease is this more difficult than in tuberculosis and especially in pulmonary tuberculosis. Some criteria for such studies have been outlined<sup>29</sup> and it is hoped that a number of institutions may succeed in carrying out observations on treated patients with constant reference to a comparable control group of patients who do not receive chemotherapy.

Progress in research on tuberculosis has been unavoidably slow and will continue at a slower pace than in the case of acute diseases. This appears inevitable in a disease such as tuberculosis of man, which shows a pronounced tendency to spontaneous healing but which may lie latent for many years. Tuberculosis of guinea pigs and of man are different diseases, even though the etiologic agent is the same, and results appear to demonstrate that clinical predictions cannot be based safely on results obtained with experimental animals. This is due in part to the mechanical handicaps against healing produced by the destructive effects of chronic tuberculosis as it frequently affects tissues and especially the lungs of human beings. Mechanical correction by methods of collapse therapy is not likely to be entirely supplanted in such cases and if an effective chemotherapeutic agent eventually should be developed, its rôle is likely to be that of an adjuvant to conventional methods of treatment.

The urgent need for more rapid methods of forecasting the chemotherapeutic potentialities of new compounds made for use against the tubercle bacillus is obvious<sup>31</sup>. The *in vitro* approach appears logical but as yet no investigator has described such a method which correlates with results *in vivo*. Serious lack of correlation has been shown in the case of 2,4'-dichlorobenzophenone<sup>32, 33</sup>. It should also be recalled that many gold compounds are effective *in vitro* but not *in vivo*. In some instances the validity of studies made *in vitro* can be questioned because cultures of rapidly growing strains of avirulent acid-fast bacilli have been employed and their genetic relationship to bacilli of tuberculosis is uncertain. Youmans<sup>34</sup> recently has demonstrated that avirulent and virulent strains of acid-fast bacilli may behave quite differently toward chemotherapeutic substances *in vitro*. His results suggest that in future efforts to develop *in vitro* tests, strains of at least standard virulence should be employed. The significance of reports of work in which

cultural methods are employed can be judged only when extensive parallel studies have been carried out with experimentally infected animals

### SUMMARY AND COMMENT

Several drugs of the sulfone series have demonstrated a striking ability to arrest tuberculosis experimentally induced in guinea pigs. The tubercle bacillus must be added to the long list of organisms amenable, at least to some extent, to the chemotherapeutic approach. Three substances, promin, diasone and promizole, have been subjected to clinical trials with mildly encouraging, but not conclusive results. Promizole has the distinct advantage of low toxicity for man but its clinical efficacy has not been adequately demonstrated at this time.

It now appears certain that none of the drugs available for chemotherapy of tuberculosis has any clinical therapeutic effect comparable to the prompt and striking results commonly observed when sulfonamide drugs and penicillin are utilized in treatment of acute diseases. It is not known whether the fact that results with tuberculosis are less striking is due (1) to peculiarities of the tubercle bacillus, (2) to the unusual tissue responses in tuberculosis, or (3) more probably to the limited chemotherapeutic properties of drugs studied thus far.

Appraisal of chemotherapy in clinical tuberculosis must await the performance of adequately controlled clinical studies or the development of a remedy so powerful that results are immediately obvious. If a chemotherapeutic agent of practical application becomes available, its existence should be announced to the medical profession through proper professional channels. In the meantime, physicians should advise their patients to accept conventional forms of treatment, especially sanatorium care and collapse therapy, the value of which has been well established.

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# BRONCHOSPIROMETRY <sup>1</sup>

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By spirometric examinations the total functions of both lungs can be studied. Bronchospirometry is a relatively recent method by which the functions and volumina of each lung are determined separately at the same time. Jacobaeus, Bjorkman and Frenckner <sup>12</sup> were the first to publish such studies in 1932. They used a double-channelled metal bronchoscope. A number of studies were done with this method by Bjorkman <sup>2</sup>, Frenckner and Bjorkman <sup>6</sup>, Jacobaeus <sup>8, 9</sup>, Bezançon, Biau, Soulas and Cachin <sup>1</sup>, Brighton and Barach <sup>3</sup>, and Jacobaeus and Bruce <sup>10, 11</sup>.

In 1939 Gebauer <sup>7</sup> reported a soft-rubber bronchial catheter, constructed for use in bronchospirometry. Before that publication we had already started to do bronchospirometric studies with a similar catheter which had been devised independently by Zavod <sup>22</sup>. The introduction of this instrument is less disagreeable to the patient than the metal bronchoscope, hence the respiratory mechanism is less disturbed and the results, therefore, are more closely comparable to those obtained by spirometry.

Results of studies with the soft-rubber catheter have been reported by Gebauer <sup>7</sup>, Leiner, Pinner and Zavod <sup>14</sup>, Vaccarezza, Lanari, Bence and Labourt <sup>18, 19</sup>, Pinner, Leiner and Zavod <sup>15</sup>, Whitehead, O'Brien and Tuttle <sup>20</sup>, Wright and Woodruff <sup>21</sup>, Steele <sup>17</sup>, and Leach <sup>13</sup>.

The catheter and the technic of its introduction have been described in detail by Zavod <sup>22</sup>. Complete local anesthesia and sedation are essential.

When the catheter is in place, the proximal openings of the two channels are connected to two spirometers, such as are described by Cournand, Richards and Darling <sup>5</sup>. The ventilation of each lung is then recorded separately and simultaneously.

Figure 1 is a tomogram showing the catheter in correct position, as it is also seen by fluoroscopy. A flexible steel plate in the tip of the catheter and the capillary air leads are radio-opaque.

On the following pages we wish to present a summary of the main results of bronchospirometric studies which were pursued at Montefiore Hospital during the last five and a half years.

## INDICATIONS AND CONTRAINDICATIONS FOR BRONCHOSPIROMETRY

Pulmonary function tests may be compared to renal function tests. In diffuse diseases of both kidneys, such as the various types of Bright's disease, we usually are interested only in the total function of both kidneys and use

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tests by which the total renal function is revealed. Correspondingly we examine the total functions of both lungs by spirometric tests in diffuse bilateral pulmonary disease, such as emphysema and pneumoconiosis. However in a unilateral or predominantly unilateral renal disease (for instance renal tumor), the functions of each kidney are studied separately. In our opinion, the same should be done in unilateral pulmonary disease, particularly preceding irreversible operations on one lung (thoracoplasty,

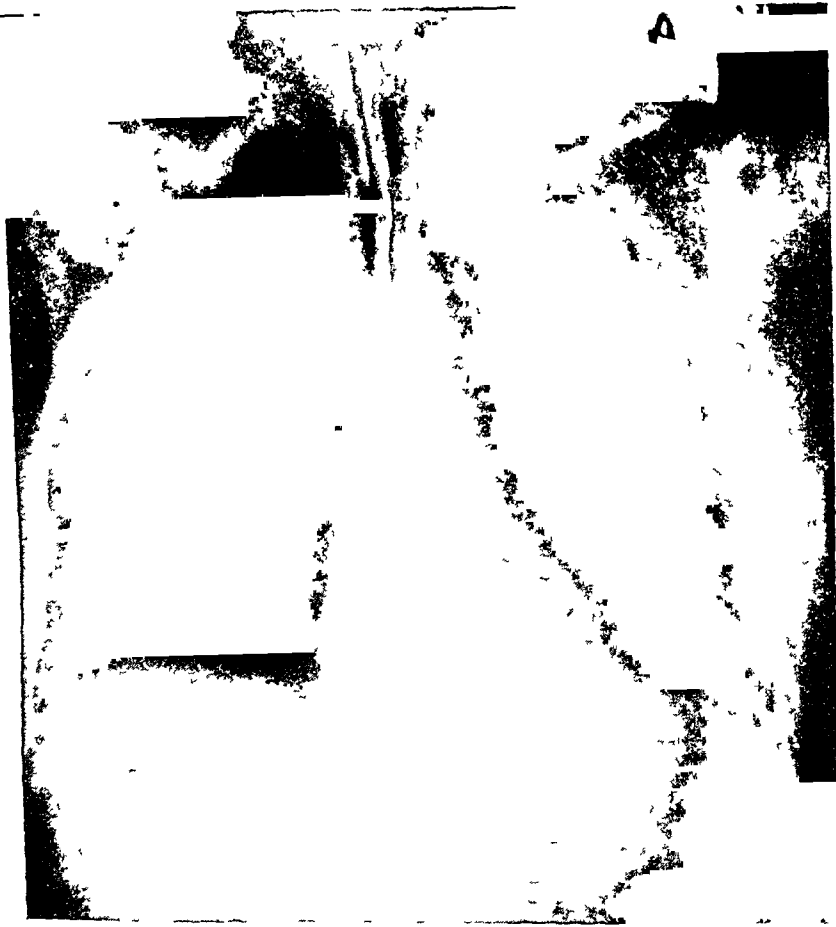


FIG 1 Tomogram showing the bronchospirrometry catheter in correct position. The flexible steel plate in the tip of the catheter as well as the capillary air leads can be seen.

lobectomy, pneumonectomy) if there is any doubt about the efficient function of the other lung. Clinical and roentgenological examinations frequently do not reveal the functional status of one lung.

Besides this practical application, bronchospirrometry permits us to study various physiopathological problems of respiration, especially those concerned with the compensatory mechanisms which are called forth in one lung by disease or operative procedures (collapse measures, lobectomy).

Contraindications to bronchospirrometry are tuberculous ulcerations of

the larynx and, to a lesser extent, of trachea or bronchi. In addition to that, patients who have high fever, who have had a recent hemoptysis, or who are otherwise very ill should not be subjected to intubation. In patients with large amounts of viscous sputum it is often impossible to obtain satisfactory records because of obstruction of the channels.

We have attempted bronchspirometry about 380 times and have obtained 270 satisfactory records. In no patient have we had a serious accident. One female who had a vital capacity of 770 c c (24 per cent of normal) became very dyspneic during induction of the tube, we would, therefore, advise against bronchspirometric studies on patients with severely depressed vital capacity. We saw several slight reactions due to cocaine.

One female patient was so excited that she hyperventilated and got a tetanic attack, trismus developed, the patient pinched the tube with her teeth and nearly choked herself, the tube was removed and the patient recovered immediately. Another female patient had a severe bronchospastic attack after the examination was over, she was relieved by adrenalin. In three patients fever and nonspecific pulmonary infiltrations appeared on the day following bronchspirometry. These infiltrations cleared within a short time and no permanent damage ensued. No spread of the tuberculous process was seen in any case. Many of our patients had two or three bronchspirometric examinations without any untoward effect.

#### RESULTS OF BRONCHOSPIROMETRY

The data which we determine by bronchspirometry for each lung are

- (1) Oxygen intake per minute,
- (2) Minute volume of respiration,
- (3) Respiratory rate,
- (4) Tidal air,
- (5) Ventilation equivalent for oxygen (that is the amount of air in liters which a lung ventilates while 100 c c of oxygen are absorbed),
- (6) Vital capacity,
- (7) Reserve air,
- (8) Complementary air.

Compared with normal respiration, the respiration through the bronchspirometry tube is modified. The changes are similar to those which are found in the breathing in stenosis. Statistical analyses of such data will be published elsewhere. Here we wish to present only those data which are pertinent for the understanding of our results.

The disturbance in ventilation and respiration caused by the introduction of the bronchial catheter is sufficiently marked to vitiate, within certain limits, the values found by bronchspirometry for pulmonary volumina, oxygen intake and minute volume. All absolute values must, therefore, be determined spirometrically. The bronchspirometric data provide the much

needed information of how the various factors are distributed between right and left lung

### COMPARISON OF SPIROMETRIC AND BRONCHOSPIROMETRIC FINDINGS WHERE THE LATTER GIVE ADDITIONAL INFORMATION

All patients in whom bronchospirometric studies were done had also spirometric examinations. In a certain number of cases only bronchospirometry revealed abnormal functions of one lung whereas the spirometric findings were normal or nearly normal. We will present a few cases out of this group.

87 M W, a 29 year old male, had a pneumothorax on his right side with 40 per cent collapse. The vital capacity on spirometry was 2,650 cc. Maximum breathing capacity divided by minute volume was 11.3, a finding which is consistent with a normal respiratory reserve. On bronchospirometry it was found that the oxygen intake of the right lung was only about one third of the total oxygen intake. In spite of a normal respiratory reserve, the right lung contributed only about 30 per cent (instead of 54 per cent under normal conditions) to the total oxygen intake.

149 A O, a 31 year old female, showed a diffuse infiltrative lesion between the apex and the second anterior rib on the left and minimal infiltrations in the right apex. The vital capacity was 3,600 cc, or practically normal, the ventilation equivalent, as found by spirometry was 3.4 l. Bronchospirometry revealed that the right lung had a vital capacity of 2,150 cc, the left lung of 1,390 cc. The ventilation equivalent of the right lung was 3.5 l, the ventilation equivalent of the left lung was 4.3 l. Bronchospirometry thus revealed definite functional damage to the left lung, whereas the findings on spirometry were practically normal.

The ventilation equivalent is one important index of respiratory efficiency. It is often found that a normal value obscures the fact that the ventilation equivalent of one lung is much increased, indicating impaired function in terms of a disturbed relation between ventilation and available pulmonary circulation. Table 1 (Pinner and Margulis<sup>16</sup>) shows examples

TABLE I  
Comparison of Ventilation Equivalent as Determined by Spirometry  
and by Bronchospirometry

Patient Number	Spirometry	Bronchospirometry	
		Left Lung	Right Lung
62	2.9	4.6	2.1
50	2.4	1.2	4.7
151	3.1	5.1	1.8
69	2.8	5.7	2.7
51	2.6	6.3	2.2
171	2.9	1.8	6.3
49	2.7	6.3	2.3
56	2.2	7.4	2.6
74	2.8	2.1	8.2
46	2.2	10.3	2.3
69	1.9	16.4	2.2

of the striking discrepancy that may exist between the ventilation equivalent, as determined spirometrically for total function and that of single lungs, as estimated bronchspirometrically. A high ventilation equivalent signifies that oxygen resorption is more damaged than ventilation, in such cases the vital capacity may be close to normal, whereas the respiratory function is severely damaged, emphasizing again that vital capacity determination per se is not a measure of respiratory function.

#### DISCREPANCIES BETWEEN ROENTGENOLOGIC AND BRONCHOSPIROMETRIC FINDINGS

The functions of a lung may be much better or much worse than one might expect from clinical and roentgen-ray findings. Jacobaeus, Frenckner and Bjorkman<sup>12</sup> pointed out in their first paper that "there is a certain lack of conformity between the results of roentgen examination and those obtained by the bronchspirometric test."

A few cases are presented in which certain bronchspirometric findings were not suspected by roentgenological and clinical observations.

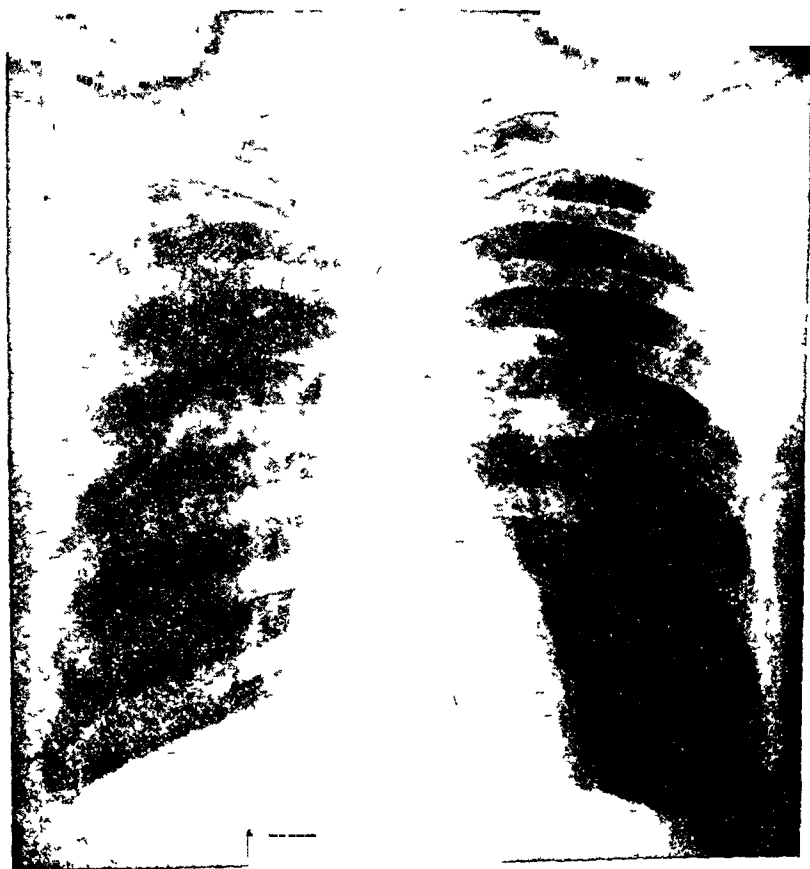


FIG 2 Chest roentgenogram of patient 72, B M Findings for left lung in per cent of  
total Oxygen intake 43, tidal air 51, vital capacity 54

72 B M was a 35 year old male Roentgen-ray examination (figure 2) showed in the right lung moderate fibrosis in the midzone and slight fibrosis of the upper half, the left lung was clear. In spite of the pathological changes in the right lung, the percentage distribution of the pulmonary volumina and the oxygen intake are about normal. The history revealed that the patient had had a pleurisy on the left seven years prior to these studies. As has been shown by Pinner, Leiner and Zavod,<sup>15</sup> pleurisy is often the cause of considerable functional damage of a lung. The right lung here compensated for the damaged left lung.



FIG 3 Chest roentgenogram of patient 150, M Y. Findings for right lung in per cent of total: Oxygen intake 58, tidal air 49, vital capacity 51.

150 M Y was a 22 year old female. In spite of mottled infiltrations on the right from apex to the fourth anterior rib and multiple small cavities (figure 3) there seemed to be no functional damage of the right lung, the distribution of the functions between right and left lung was approximately the same as we would expect if both lungs were normal. This shows that parenchymal lesions frequently do not demonstrably impair pulmonary functions.

264 R T was a 23 year old male. The figures (figures 4a and b) given were found before and after induction of pneumothorax. In spite of a reduction of the vital capacity we notice an increase of the oxygen intake on the collapsed side. This might have been caused by reduction of dead space and more efficient utilization of the functioning portions of the lung. This question has been previously discussed (Leiner, Pinner and Zavod<sup>14</sup>).

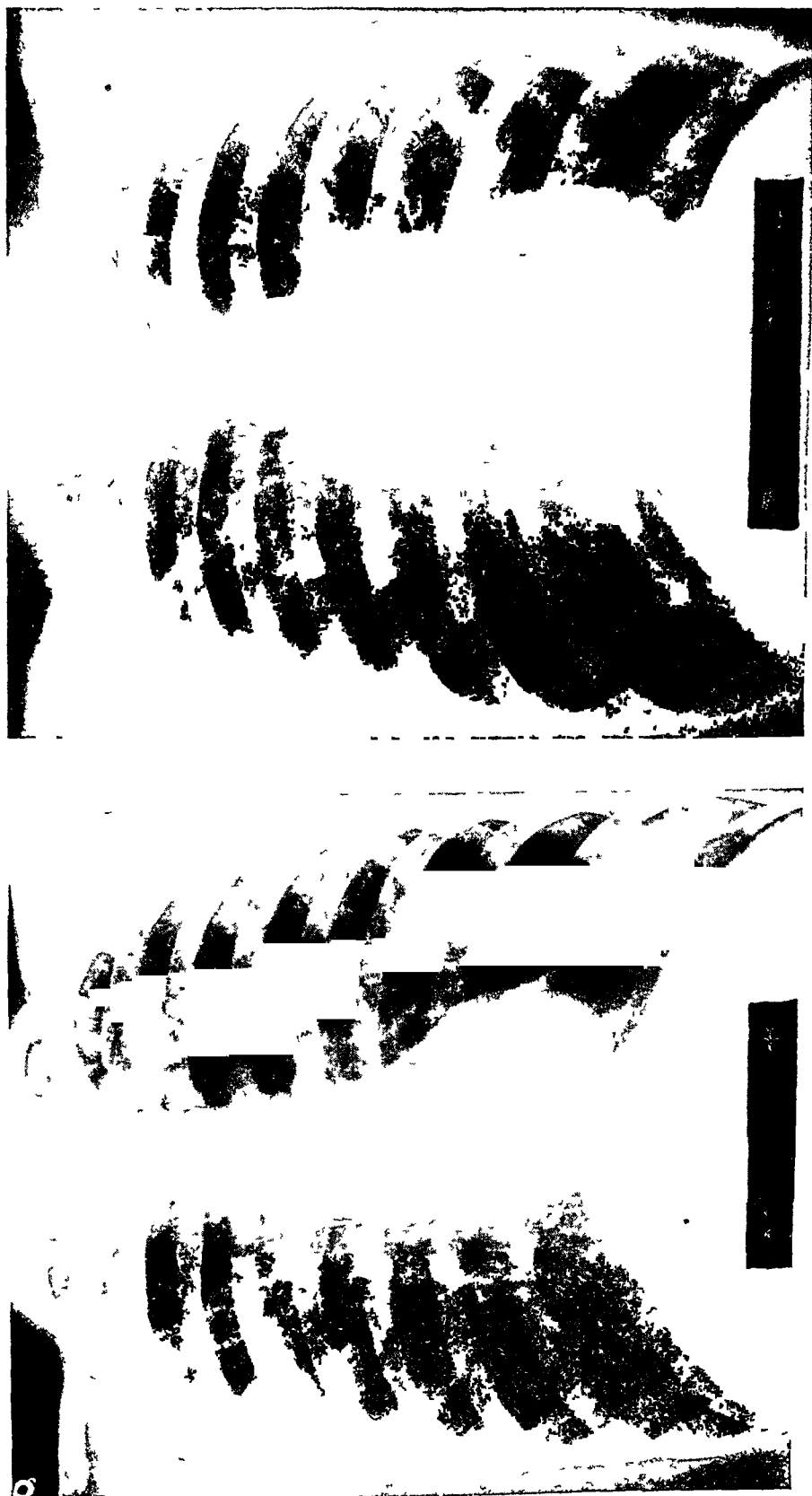


FIG 4 Chest roentgenogram of patient 264, R T, before and following induction of right pneumothorax. Findings before pneumothorax for right lung in per cent of total Oxygen intake 29, tidal air 50, vital capacity 50. After induction of pneumothorax, oxygen intake 44, tidal air 46, vital capacity 33.

## LUNGS WITH VERY POOR FUNCTIONS, LUNGS WITH STRICTLY PARENCHYMAL LESIONS, REEXPANDED LUNGS

Theoretically, according to Bjorkman,<sup>2</sup> the left lung contributes 46 to 47 per cent of the total oxygen intake. In order to find out what the causes of particularly severe functional damage were we selected patients in whom the oxygen intake of one lung was only 25 per cent or less of the total oxygen intake. It was found that each of these patients had pleural involvement—pneumothorax followed by fibrothorax, pleural obliteration, pleuritis. This was often only revealed later when attempts at inducing a pneumothorax were unsuccessful because of pleural obliteration. Three patients in this series had had phrenicectomy. A paralyzed diaphragm apparently contributes considerably to impairment of function (Jacobaeus<sup>8,9</sup>, Cournand and Richards<sup>4</sup>). In contrast, many lungs with active parenchymal lesions without pleural involvement show relatively little functional damage even if the parenchymal lesions are extensive. It is of great practical importance that pleural involvement which cannot always be diagnosed by roentgenologic examination may lead to more severe functional damage than do much more obvious parenchymal lesions.

### EFFECT OF COLLAPSE THERAPY ON PULMONARY FUNCTION

*Pneumothorax.* We studied 18 patients before and several months after the induction of unilateral pneumothorax. The average functional changes in the collapsed and contralateral lungs were as follows. In the collapsed lung there was an average decrease of 35 per cent of oxygen intake, the minute volume decreased nearly 20 per cent (note that oxygen intake drops relatively more than minute volume<sup>1</sup>), the vital capacity was reduced by 45 per cent, the reserve air by 63 per cent, the complementary air by 45 per cent, the tidal air by 17 per cent, the ventilation equivalent rose by 27 per cent from 2.9 l to 3.7 l.

In the contralateral lung, the oxygen intake rose 30 per cent, the minute volume 16 per cent, the vital capacity, reserve air and complementary air dropped less than 10 per cent. The tidal air rose by 20 per cent and the ventilation equivalent decreased by 26 per cent from 4.2 l to 3.1 l.

On either side, the tidal air presented a larger part of the vital capacity in the presence of a pneumothorax than before induction of the pneumothorax, indicating a diminished ventilatory reserve.

In analyzing these average values it must be stressed that a considerable scattering of figures exists, as one might well expect in a group of patients who were not homogeneous as to duration and extent of pneumothorax, amount of involvement in the collapsed and in the contralateral lung and as to the presence of adhesions, mobility of mediastinum, etc. However, the average values quoted are indicative of the general trends.

The important deductions to be made are as follows



(1) Collapse (by pneumothorax) reduces the oxygen intake of the collapsed lung, this reduction is caused partly by a decreased minute volume and partly by a less efficient use of the ventilated air, as indicated by an increase in ventilation equivalent

(2) The reduction in oxygen intake is compensated for by an increased intake of oxygen through the contralateral lung

(3) This increase is achieved by some increase in the minute volume, but the increase in minute volume (a measure of ventilatory work) is considerably smaller than the increase in oxygen intake (the average being 16 per cent as against 30 per cent) A better utilization of the ventilated air, as indicated by a drop of the ventilation equivalent, is a second factor in compensation

(4) In a large proportion of cases of unilateral pneumothorax, the contralateral effect of collapse is manifested by the reduction in the vital capacity and its subdivisions of the contralateral lung

The reduction of function in the collapsed lung is compensated for not simply by a commensurate increase of the ventilatory work of the contralateral lung but, to an important degree, the compensation is achieved through a cardiovascular factor This observation provides a sound physiological basis for the clinical experience that "the burden on the contralateral lung" is not as serious as it was assumed to be in the early phase of pneumothorax work

According to animal experiments and clinical observations, in the presence of a normal contralateral lung, a normal cardiovascular system and a fixed mediastinum, ventilation remains competent at least under basal conditions, following the removal of one lung From this it follows that, if a patient with unilateral pneumothorax is dyspneic at rest, the cause is not likely to be found solely in the degree of pneumothorax collapse It has to be looked for in the contralateral lung (pleural obliteration, emphysema or other pathological pulmonary conditions) or in the cardiovascular system, provided a mobile mediastinum, causing too much contralateral collapse, can be excluded Ipsilateral or contralateral bronchial stenosis must be ruled out as well

A large number of lungs which were "reexpanded" following pneumothorax treatment were studied Many of these showed severely impaired function There are essentially two causes for this condition (1) incomplete reexpansion of the lung with contraction of the hemithorax, shift of the mediastinal structures to the pneumothorax side and emphysema of the contralateral lung (i.e., different degrees of fibrothorax), and (2) pleural obliteration with the adverse functional effects, mentioned before The first condition is clinically and roentgenologically obvious, the second is not and is, therefore, deceiving

*Thoracoplasty* We have studied 26 patients by bronchspirometry before and several months following the completed operation The total pulmonary function, as determined by spirometry, was as follows With very

few exceptions the oxygen intake did not show any significant change. The minute volume, again with few exceptions, did not change materially. The vital capacity and its subdivisions were markedly decreased in practically all cases. The ventilatory reserve, as indicated by the maximum breathing capacity, was decreased by more than 10 per cent in half the patients.

The average decrease of oxygen intake in the collapsed lung of 18 thoracoplasty patients was 20 c.c. The maximum decrease of oxygen intake was 100 c.c., but in seven of these 18 patients the decrease was less than 10 c.c. (in two there was an actual increase).

Since the average decrease of oxygen intake in the lungs collapsed by thoracoplasty is quite small, the compensatory mechanism is less obvious than in pneumothorax. However, the study of individual cases indicates that the principal mechanisms are the same as in pneumothorax.

In comparing the two collapse procedures, it is probably significant that in lungs collapsed by pneumothorax, the average of the ventilation equivalent rose from 2.9 l to 3.7 l whereas in lungs collapsed by thoracoplasty, it did not show any significant change (4.1 l before, 4.0 l after). In the latter group of patients, the ventilation equivalent decreased very markedly in a few patients (i.e., from 10.3 l to 1.9 l, from 5.4 l to 3.1 l), indicating that thoracoplasty may bring about a particularly successful selective collapse of functionally severely impaired portions. Much larger series of patients must be studied in order to decide whether the apparent functional superiority of thoracoplasty over pneumothorax is real or simulated by random sampling.

#### INFLUENCE OF DIFFERENT POSTURES ON PULMONARY FUNCTION

Jacobaeus did repeated bronchspirometric studies on normals when they were lying on their back and on either side. He found that the ventilation and the oxygen consumption were higher on the side on which the subject was lying. Gebauer saw no change of the function of the right side and a slight decrease of the tidal air of the left side when a patient was turned on his left side. Vaccarezza, Lanari, Bence and Labourt<sup>10</sup> claim that the lung on the side on which the patient is lying has a higher oxygen intake, minute volume, vital capacity and complementary air than the other lung. Only the reserve air increased in the latter.

In table 2 vital capacities for each lung in six patients are given, measured in different postures of these patients. The distribution of the vital capacity between both lungs did not change consistently nor significantly when the patients changed their position from lying on the back to lying on either side. We do not have enough studies of the other respiratory data to be able to say whether or not they are influenced by change of posture. It is usually not possible to leave the bronchspirometry tube in place long enough to get good records in each position.

TABLE II  
Bronchspirometric Determinations of Vital Capacity in Different Positions

Patient Number	Position	Vital Capacity c c	
		Right	Left
54	Lying on back	830	1040
	Lying on right	870	1120
	Lying on left	750	1160
55	Lying on back	1490	890
	Lying on right	1430	890
	Lying on left	1570	770
56	Lying on back	1680	430
	Lying on right	1820	410
	Lying on left	1780	460
62	Lying on back	1180	290
	Lying on right	1180	290
	Lying on left	1240	330
284	Lying on back	1510	1410
	Lying on right	1390	1280
	Lying on left	1450	1490
105	Lying on back	810	1530
	Lying on right	770	1470

### INFLUENCE OF WEIGHT AND STRAPPING ON PULMONARY FUNCTION

It is commonly believed that the motion of one lung can be reduced when heavy weights are placed upon the respective side of the chest or when one hemithorax is strapped by several layers of adhesive tape. It seemed to be of interest to see what functional changes occur in lungs under such conditions.

In patients in whom the routine bronchspirometric studies had been done sandbags weighing six to 20 pounds were put on one side of the chest. The results of such studies on seven patients are presented in table 3. Moderate changes in oxygen consumption should not be taken into account, since records of only brief duration could be taken, a fact which makes an exact calculation of the oxygen consumption impossible. However, it is obvious that the oxygen consumption practically never decreases in the weighted side. Minute volume and tidal air increase more often than not. The vital capacity remains unchanged. Without any doubt, putting a weight on one side of the chest does not achieve a shifting of the ventilatory nor of the respiratory work from one lung to the other. If the excursions of the chest wall are diminished by the weight, the diaphragm increases its excursions. Ventilation (minute volume, tidal air) increases on either side, owing to the increased work the chest has to do in order to lift the weight.

In a recent paper, Leach<sup>13</sup> reports that he saw decrease of oxygen absorption in lungs which were compressed by sandbags. The observation

TABLE III  
Effect of Sandbags on Ventilatory and Respiratory Function on Single Lungs

Patient Number	Weight of Sandbag and Side	Right Lung					Respirations per min	Left Lung				
		O intake per min c c	Minute Volume c c	Tidal Air c c	Ventila tion Equiv alent l	Vital Capacity c c		O intake per min c c	Minute Volume c c	Tidal Air c c	Ventila tion Equiv alent l	Vital Capacity c c
72	18 lbs on right	196	4630	165	2 0	1390	28	148	4580	163	2 7	1800
	18 lbs on left	203	5920	212	2 5	1330	28	175	6460	231	3 2	1700
95	10 lbs on right	185	5120	197	2 4	1330	26	148	5920	228	3 4	
	10 lbs on left	95	3270	252	3 0	1260	13	200	3840	296	1 7	2110
170	20 lbs on right	95	4020	211	3 7	1260	19	200	3840	202	1 7	2110
	20 lbs on left	95	4020	251	3 7	1260	16	200	3840	240	1 7	1930
174	20 lbs on right	203	6040	224	2 6	1530	27	88	4120	152	4 1	540
	20 lbs on left	210	5490	211	2 3	1620	26	86	3840	148	4 0	480
224	20 lbs on right	191	5490	211	2 5	1530	26	73	3840	148	4 6	500
	20 lbs on abdomen	218	4610	329	1 8	1700	14	124	4170	291	2 9	1590
284	6 lbs on right	150	4390	439	2 5	1640	10	103	4120	412	3 4	1530
	8 lbs on right	150	4780	341	2 7	1620	14	150	4390	342	2 5	1590
409	10 lbs on right	150	4120	374	2 3	1590	11	113	3840	349	2 9	1530
	18 lbs on left	133	4280	285	2 8	700	15	162	6040	402	3 2	1280
284	6 lbs on left	143	4390	314	2 7	700	14	190	6540	471	3 0	1280
	8 lbs on left	133	4390	274	2 9	700	16	171	7140	446	3 6	
409	10 lbs on left	143	4390	274	2 9	700	16	162	7140	446	3 8	
	18 lbs on left	152	4940	291	2 8	670	17	190	7720	454	3 5	
284	6 lbs on abdomen	143	4390	259	2 7	670	17	162	7720	454	4 1	1240
	15 lbs on right	133	5490	305	3 6	2630	18	171	8780	488	4 5	620
409	16 lbs on right	87	4580	268	4 5	1510	17	105	4670	274	3 8	580
	16 lbs on left	112	4660	389	3 5	1510	12	132	4390	366	2 9	1410
284	16 lbs on abdomen	112	4660	359	3 5	1510	13	150	4390	338	2 5	1370
	15 lbs on right	112	4940	412	3 8	1450	12	132	4390	366	2 9	1430
409	15 lbs on right	328	6980	465	1 9	2630	15	61	3050	203	4 3	
		324	8320	520	2 2	2490	16	57	3230	202	4 9	

that sandbags on one hemithorax do not decrease ventilation on that side should not necessarily be interpreted as meaning that such procedures are therapeutically without value, since they may well help to enforce more complete rest of the patient as a whole

In two experiments (174, 284) sandbags (weighing 20 pounds and 16 pounds respectively) were put on the abdomen. This had no effect on oxygen intake, minute volume and vital capacity of either lung

In three patients one hemithorax was strapped firmly with adhesive tape after routine bronchspirometric records had been taken (table 4). In one

TABLE IV  
Effect of Strapping of One Hemithorax on the Ventilatory and Respiratory Function of Each Lung

Patient Number	Side Strapped	Right Lung					Respirations per min	Left Lung				
		O <sub>2</sub> intake per min cc	Minute Volume cc	Tidal Air cc	Ventilation Equivalent l	Vital Capacity cc		O <sub>2</sub> intake per min cc	Minute Volume cc	Tidal Air cc	Ventilation Equivalent l	Vital Capacity cc
315	none left	112	4940	198	3.8	1370	25	146	5210	209	3.1	1860
		112	4120	173	3.1	1040	24	150	4940	206	2.8	1370
326	none right	80	4190	174	4.5	1060	24	99	3970	165	3.4	1240
		99	3430	137	3.0	990	25	136	4350	174	2.7	1180
109	none right	219	4890	408	1.9	1720	12	94	4350	362	4.0	890
		225	5440	362	2.1	1800	15	103	4890	326	4.1	950

case (315) the vital capacity decreased on both sides practically by the same percentual amount (right, 24 per cent, left, the strapped side, 27 per cent). Only in one case (326) did minute volume and tidal air decrease somewhat on the strapped side and increase on the free side. From these findings we can conclude that strapping of the chest does not diminish pulmonary motion.

#### SUMMARY

By bronchspirometry functions and volumina of each lung are determined separately and simultaneously. The use of a soft rubber tube, instead of the metal bronchoscope, has made the method less uncomfortable for the patient and the results more reliable. Bronchspirometry is indicated whenever an irreversible operation on one lung is contemplated in order to determine the functional capacity of the contralateral lung. It also permits the study of various physiopathological problems.

No serious complication was seen in about 270 bronchspirometric examinations. The significance of the data obtained by bronchspirometry is discussed.

Spirometry may give nearly normal findings in patients in whom bronchspirometry reveals extensive damage of one lung and compensatory changes

in the other lung. Roentgen-ray and clinical findings do not permit definite conclusions as to pulmonary function.

Pleural involvement often causes severe functional damage of the lung, whereas parenchymal lesions may have relatively little effect on pulmonary function.

During pneumothorax treatment, the collapsed lung shows the following changes: decrease of oxygen intake, minute volume, tidal air, vital capacity, reserve air and complementary air, increase of ventilation equivalent.

Compensation is achieved by an increase of the oxygen intake in the contralateral lung. This is done only in part by increased ventilation, oxygen intake is further increased by a better utilization of the ventilated oxygen, i.e., a decrease of the ventilation equivalent.

The contralateral effect of unilateral pneumothorax is manifested by a decrease of the vital capacity, reserve and complementary air of the contralateral lung.

Thoracoplasty causes similar functional changes as does pneumothorax but, on the average, these changes are less severe following thoracoplasty than those during collapse by pneumothorax and, at least in some cases, less severe than those in lungs following the abandonment of pneumothorax.

Lungs reexpanded following pneumothorax treatment frequently show extensive functional impairment.

Change in the patient's posture from the recumbent to the left or right side does not affect the percentage distribution of the vital capacity between the left and right lung.

Attempts at "immobilizing" a hemithorax by sandbags weighing up to 20 pounds and by strapping with adhesive tape do not achieve a reduction of the ventilation or respiratory work of the underlying lung.

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# CASE REPORTS

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## DUODENAL ULCER WITH PERFORATION FOLLOWING A CUTANEOUS BURN, REPORT OF A CASE \*

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*Historical* "Dupuytten, in 1832, 10 years before Curling's article appeared, called attention to the change in the 'intestinal canal' which followed burns. Violent congestion, severe gastroenteritis, and 'more or less deep ulceration' were the conditions he found, depending on the length of time the patient had survived the accident. Long, in 1840, described two instances of fatal burns in which perforation of duodenal ulcers occurred" †

The term "Curling's ulcer," as Keeley<sup>1</sup> points out, has been adopted largely because his was the largest collection of cases yet published, and because his original paper described lesions occurring specifically in the duodenum, the site of the great majority of reported cases.

*Incidence* Statistics vary greatly as to the incidence of duodenal ulcers following burns. There are many instances in which men with wide necropsy experience have never seen a case. In a report of 104 cases of cutaneous burns, Bancroft and Rogers<sup>2</sup> found that 28 per cent of the entire series were fatal, yet no instance of gastrointestinal ulceration was noted. Thirty-four per cent of their cases were under 10 years of age. Harris,<sup>3</sup> in a series of 138 fatalities, reported one death due to ulceration. Levin<sup>4</sup> found this lesion once in 13 years of autopsies. There is no record of a single case of gastrointestinal ulceration in a series of 171 cases of burns and scalds seen at Peter Bent Brigham Hospital in a 24 year period ending in 1937. Following the recent Coconut Grove disaster, 39 patients were sent to Massachusetts General Hospital. Autopsies were performed on six of these, three being dead on arrival, and three surviving from 40 to 62 hours. The gastrointestinal pathologic change was that of congestion and petechial hemorrhages in the fundic portion of the stomach and in the duodenum, though no ulceration was reported<sup>5</sup>. In Harkins'<sup>6</sup> exhaustive review of the literature in 1938, the first in 45 years, he included the following table. He concludes that the average of 3.8 per cent is probably near the correct figure for the incidence of ulcers following burns, but points out that there are many factors involved which make the statistics difficult to interpret.

These ulcers are commonest in children, the average age in Curling's series being 10.8 years. In Harkins'<sup>6</sup> collection of 94 necropsied cases since 1823, the average in 74 cases was 14.6 years, though cases have been reported in individuals 70 years of age. The age of the patient in our case was 68 years. In 65 of Harkins'<sup>6</sup> cases, 72 per cent were females.

The ulceration may occur at any time following the burn, though Maes<sup>7</sup> asserts that they are usually considered a late complication. McLaughlin<sup>8</sup> states

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† Quoted from KEELEY<sup>1</sup>.



TABLE I  
Percentage of Duodenal and Gastric Ulceration Following Burns in  
Necropsied Cases

Author	Date	Number of Deaths Due to Burns	Number of Ulcers	Percentage Incidence of Ulcer
Long	1840	22	2	8.2
Curling	1842	11	4	36.4
Hewett	1848	17	3	17.7
Erichsen	1895	94	2	2.1
Simmonds	1898	50	2	4.0
Gruber (Strassburg)	1913	22	3	13.6
Gruber (Munich)	1913	19	9	0.0
Stewart	1923	115	2	1.7
Ronchese	1924	34	1	2.3
Harris	1929	138	1	0.7
Riehl	1930	152	5	3.3
Harkins	1937	4	1	25.0
		680	26	3.8

they usually appear in from two to 17 days following the burn, the average time being six to 12 days. Harkins<sup>6</sup> found that in 31 cases where the ulcer was associated with definite perforation or hemorrhage, death occurred in 12.8 days. Instances of ulceration occurring as early as 18 hours<sup>4</sup> and as late as 100 days<sup>9</sup> have been reported.

*Etiology.* The cause of "Curling's ulcer" is still awaiting experimental proof. The theories which have been advanced are limited only by the number of observers. Some of those which have received the most support are the following:

(1) "Curling suggested that Brunner's glands were called upon to perform the excretory functions for which the burned skin was incapacitated." (Quoted from Keeley<sup>1</sup>)

(2) The toxic theory, supported by Maes,<sup>7</sup> Robertson and Boyd,<sup>10</sup> and others, assumes that a toxin is carried to the intestines by the blood. Harris<sup>3</sup> feels that the pancreatic ferments digest and form ulcers in areas of necrosis formed by the burn toxins.

(3) McLaughlin's<sup>8</sup> experimental work of partially damaging the adrenals of 21 dogs produced ulceration in the small bowel of 17 of them, but no ulceration of the stomach was observed.

(4) The embolic theory with the infarcted area becoming necrotic and falling away is said to have been supported by Bilstroth. Others, however, have called attention to the fact that emboli never occur in the duodenum without occurring also in the stomach, and point out also that the obstructed vessel has never been found.

(5) The subsequent development of duodenal ulcers following infection of the burned area has been noted by many. Stewart<sup>11</sup> states that "bacterial infection and intoxication is undoubtedly the most important direct cause of acute gastric and duodenal ulcers." He feels that ulcers following burns are less frequent than formerly because of asepsis. The extensive report of Perry and Shaw<sup>12</sup> includes 18 cases of duodenal ulcers collected from the Guy's Hospital records and three from other sources. The Guy's Hospital cases gave a ratio

of 18 septic ulcers to 52 from all causes and they came to the conclusion that duodenal ulceration is associated with septic conditions as frequently as it is with burns. They felt that the mechanism of production of the ulceration was the same in both cases.

(6) Recent experimental work by Necheles and Olson<sup>13</sup> may throw some light on the pathogenesis of this type of ulcer. In their experiments on dogs, they found that the volume of gastric secretion following burns was increased considerably if intravenous infusions of a saline-glucose solution were given, whereas there was no appreciable increase if no fluids were administered. Feeding before the burn resulted in an increase in the volume and the free acid of the gastric secretions. They suggest that these findings may have a relation to burns in human beings who at the time of the burn are generally in the absorptive phase of digestion and usually receive large amounts of fluids by mouth or by clysis. They found also a marked increase in the gastric motility which they conclude cannot be due to histamine for it is abolished by small amounts of atropine. They feel that this points to the presence of compounds of the nature of acetylcholine which may be liberated by the burn or that the acetylcholine-splitting esterase may be inhibited by the burn.

*Pathology* In 1926, Pack<sup>14</sup> described the histopathology of these lesions conclusively. Duodenal ulcers following burns, he says, are generally single but may be multiple. The location varies, some pathologists believe generally in the upper transverse duodenum, and others find them in the descending part of the duodenum, close to the bile duct. The ulcers vary in size from a pinhead to a quarter. The amount of tissue lost may be great or slight as in some cases the lesion is but a mere erosion, whereas in others it is a rapidly sloughing, perforative process. The shape of the ulcer is irregular and dentate or long and narrow, occasionally circular. The edges are sharply and cleanly cut, the base is clean and grayish, and there may not be much inflammation at the margin. It is frequently funnel-shaped owing to a loss of more mucous membrane than muscle tissue. The outcome is perforation, hemorrhage, or spontaneous healing.

#### CASE REPORT

The patient, a 68 year old white male, presented a history which went back to May, 1942, at which time he noticed some swelling of his legs. This became progressively worse and he entered the hospital November 14, 1942, with a chief complaint of swelling of his legs and belly. He had been troubled with dyspnea and orthopnea and had had some spells of palpitation. Regardless of treatment with digitalis, all the above symptoms had progressed. There had been no precordial pain but he had had occasional attacks of suffocating pain. There had been a weight loss of 30 pounds since May 1942, since which time his appetite had been poor. There had been occasional white colored stools. Further symptoms by systems were non-contributory.

He had had scarlet fever and otitis media. Pertinent family history was that his father died of cancer of the stomach and a sister died of diabetes.

Physical examination at the time of admission showed a fairly well developed white male of about stated age, with evidence of recent weight loss. He appeared anxious about his condition. Pertinent physical findings were fine, moist râles over the entire chest on auscultation. The apex of the heart was in the sixth interspace, 10 cm to the left of the midsternal line outside the midclavicular line a mitral

systolic murmur was present. The abdomen was somewhat distended and a fluid wave was elicited. The liver edge was palpable 3 cm below the right costal margin. The extremities were edematous. The pulse rate was 80, respirations 20, temperature 97.8° C, and the blood pressure 140 mm Hg systolic and 90 mm diastolic. An impression was made of rheumatic heart disease with cardiac enlargement, mitral insufficiency, decompensation, and with a functional capacity of four.

The urine contained a few finely granular casts, but was otherwise negative. The hemoglobin was 91 per cent, the red blood cells, 4,570,000, and the white blood cells, 7,800. A chest film showed some congestion and marked enlargement of the heart to the left. An electrocardiogram taken on admission showed a rate of 82 per minute with an occasional premature contraction. The PR interval was prolonged. The QRS complex was at the upper limit of normal and was slurred. There was a left axis deviation and the ST segment was off the isoelectric line.

Treatment consisted of bed rest, proper digitalization, diuretics, and a salt free diet. He progressed very satisfactorily and was discharged December 2, 1942, with orders for one-half cat unit of digitalis per day. The electrocardiogram showed no appreciable change.

The patient was next seen on July 9, 1943, when he entered the hospital as an emergency following a gasoline burn on his left leg. Since his previous hospitalization, he had had but little dyspnea but had had some precordial pain on the right. There had been no orthopnea or ankle edema. There had been an additional weight loss of 10 pounds and some constipation. He had noticed a slight swelling in the right groin which was diagnosed by his family physician as a hernia and he had been wearing a truss. There were no additional complaints.

The patient appeared in much pain. There were first and second degree burns on the tip of the nose and both ears. The lungs were clear. The heart sounds were of good quality with regular rhythm. The apex was in the sixth interspace, 10 cm from the midsternal line. Outside the midclavicular line there was a blowing systolic murmur heard best at the apex. There was no ascites or edema. There were second and third degree burns over the entire lower left leg extending down over the heel and covering most of the dorsum of the foot. The burn extended over the popliteal space up to one-third of the upper leg posteriorly. The blood pressure was 138 mm Hg systolic and 80 mm diastolic, temperature 98.6° C, respirations 34 per minute, and the pulse 116 per minute.

Blood studies on admission showed a red cell count of 4,970,000 and a white cell count of 17,400, with a hemoglobin of 103 per cent, values which were quite constant for his hospital stay. The urine was negative. An electrocardiogram was not taken.

Treatment consisted of immediate application of sulfadiazine ethanamide to the burned areas, repeated at one-half hour intervals. In three days, a satisfactory eschar was formed. He was placed on a soft diet which he took well after the first few days. Aside from some urinary difficulties which he experienced for a few days, it was felt that his progress was very satisfactory, and he had no complaints except pain at times in the burned leg. Due to flexion, it was difficult to keep the eschar intact over the popliteal area and upper leg, so vaseline gauze dressings were applied to those areas on the tenth hospital day. The patient was allowed up in a wheel chair following the eleventh day and on the twentieth hospital day, he was allowed to take a tub bath to try to loosen the eschar. On the twenty-third day, wet dressings were applied to the leg and saturated regularly with physiological saline in a further attempt to loosen the eschar, small pieces of which were removed from the edges as they became less adherent.

At 2:00 p.m. on his twenty-third hospital day, he complained of nausea and there was emesis of undigested food. It was felt that this might be the first sign of too much digitalis and it was discontinued.

At 9 00 p m of the same day, the patient complained of a sudden, severe pain in the epigastrium which radiated to the right scapula and to his back in general. His skin was cold and beads of perspiration stood out on his forehead. The abdomen had a board-like rigidity, slightly more on the right than on the left. There was a marked pulsation over the precordium though the heart tones were of poor quality. The pulse was weak. The blood pressure was 110 mm Hg systolic and 90 mm diastolic. The clinical picture appeared to be that of acute cholecystitis, a coronary attack, or a perforated viscus. A pearl of amyl nitrite brought no relief and  $\frac{1}{4}$  gr of morphine sulphate with  $\frac{1}{150}$  of atropine was administered by hypodermic.

On the twenty-fourth hospital day the blood pressure was 40 mm Hg systolic and 20 mm diastolic and the pulse could not be felt. The abdomen had lost the board-like rigidity but was still firm. The temperature was  $95.8^{\circ}$  C. The pain was most severe in the right upper quadrant. There was marked hyperresonance on the right extending up to the fifth rib and a flat plate of the abdomen disclosed a large gas bubble under the diaphragm. The blood pressure was low all day, the patient continuing to be in extreme shock. Later in the day, he complained of severe pain in the lower abdomen and physical examination revealed a markedly dilated stomach. During an attempt to insert a Levine tube, the patient went into complete collapse and died at 7 30 p m on the twenty-fourth hospital day.

#### NECROPSY REPORT

*Gross Examination External Examination* The body was that of a 68 year old man weighing 100 pounds and 168 cm in height. The subcutaneous fat was generally deficient over the limbs and thorax. The pupils were equal and measured 5 cm in diameter. There were complete upper and lower dentures. The left leg was covered by a thick, tough, grayish eschar extending from below the knee to the level of the malleoli.

*Internal Examination Thorax* The pleural surfaces were smooth and glistening. The lung tissue was well aerated and normal grossly and on cut section.

*Heart* The pericardial surfaces were smooth and glistening and the pericardial sac contained about 20 c c of clear yellow fluid. The heart weighed 490 grams. The right ventricle measured 7 mm in thickness, the left, 15 mm. The mitral valve was slightly dilated but there was no gross evidence of any involvement of its leaflets or those of the tricuspid. The aortic valves were normal except for two small, calcified nodules, 1 by 2 mm in size at the base of the right anterior cusps. The coronary vessels were patent and only slightly sclerotic.

*Abdomen* The abdomen was slightly distended and on being opened, some gas escaped from the cavity. There were about 500 c c of a dark brown, thin, opaque fluid in the abdominal cavity. The intestinal surfaces were generally dulled and injected, the latter being most marked over areas of the small bowel lying in the false pelvis. There was an area of inflammation and fibrous adhesions lying between the anterior, superior aspect of the pylorus, the falciform ligament, and the underside of the anterior edge of the left lobe of the liver. Pressure on the stomach caused brownish, opaque fluid to appear in this region. Blunt dissection revealed a punched-out round hole, 5 mm in diameter, on the anterior, superior aspect of the duodenum, just about at the junction of the pyloric sphincter and extending through all coats of the intestine (figure 1). This ulcer showed no inflammation and little evidence of fibrosis and scarring (figure 2). About one-half inch distal, there was another area of superficial ulceration with an inflammatory margin about 5 mm in diameter (figure 2). The mucosa of the stomach along the lesser curvature showed multiple pin-point ulcerations and hemorrhages in the mucosa (figure 3).

*Intestines* The serosa of the intestines showed patchy areas of inflammation throughout especially so in those portions of the ileum lying low in the abdomen. There was not much gas or fecal material in the intestines. There was no evidence of mesenteric thrombosis.

*Spleen* The spleen weighed 120 grams and was grossly congested. On cut surface, there was some evidence of fibrosis and the cortex bulged slightly beyond the capsule. The capsule was not thickened.



FIG 1 Duodenal ulcer, serosal surface

*Kidney* The right weighed 110 grams, the left, 115 grams. There were several cysts ranging in size from 5 mm to  $1\frac{1}{2}$  mm in diameter in both kidneys. There was little evidence of any lobulation and the cortex was not thickened. There was good differentiation of the markings. There was some evidence of arteriosclerotic patches over which the capsule was adherent. The right kidney showed an area of about  $\frac{3}{4}$  by 1 cm where the cortex was thinned and had been replaced by fibrous tissue.

*Liver* The liver was not removed. It was normal in size and the edge was sharp but somewhat softened. The cut surface showed gross evidence of congestion.

*Anatomical Diagnosis* (1) Acute ulceration of the duodenum with perforation

(2) Generalized peritonitis (3) Cardiac enlargement (4) Renal arteriosclerosis and polycystic kidney disease

*Microscopic Examination Kidney* The interstitial tissue showed extensive fibrosis and infiltration of lymphocytes, the glomeruli and tubules showed atrophic changes. The interlobular arteries were thickened and the lumina of some were occluded. Some of the glomeruli were completely hyalinized.



FIG 2 Duodenal ulcer, mucosal surface

*Liver* The liver was congested. The liver cells showed cloudy swelling and many contained a fine, greenish-yellow pigment. The capsule was thickened and infiltrated with lymphocytes except superficially where there were a few polynuclear neutrophils.

*Pancreas* The pancreas was somewhat atrophic and showed postmortem autolysis. The pancreatic duct contained bile pigment and the wall of the duct was infiltrated with inflammatory cell elements. The interstitial tissue was infiltrated with lymphocytes.

*Intestines* The serosa was coated with fibrin and contained polynuclear neutrophils

*Heart* The myocardium was infiltrated with a few polynuclear neutrophils and lymphocytes. Some areas showed marked fibrosis and were infiltrated with lymphocytes and a few polynuclear neutrophils. Some of the muscle fibers were hypertrophied and others were atrophied.

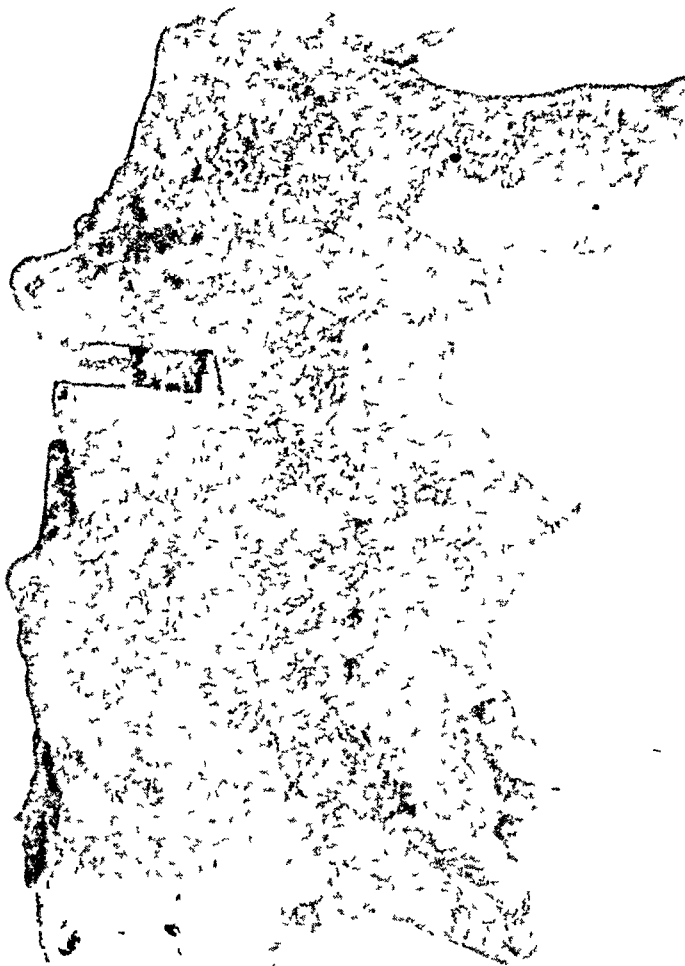


FIG 3 Congestion and punctate hemorrhages of gastric mucosa

*Spleen* The spleen showed evidence of congestion

*Skin* The subcutaneous tissue showed necrosis with organizing thrombi in some of the larger vessels

*Lung* The alveolar walls were thin and the alveolar spaces were large

*Microscopic diagnosis* (1) Acute peritonitis (2) Chronic myocarditis (3) Subacute hepatitis (4) Marked renal arteriosclerosis (Microscopic examination by Dr Pessin)

## SUMMARY

A general discussion of Curling's ulcer has been presented from the standpoint of the history, the incidence, the pathology, and some of the theories regarding the etiology of this lesion. Some of the recent experimental work has been included. A case of Curling's ulcer is presented which is of particular interest because of the fact that the burn was not of great extent, because there were no premonitory symptoms of the developing ulcer, and because of the diagnostic difficulties encountered due to previous cardiac and gall-bladder disease.

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## LONGEVITY WITH METASTATIC CARCINOMA OF THE STOMACH \*

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THERE is considerable evidence that carcinoma of the stomach may manifest itself as a disease of marked chronicity<sup>1</sup>. Subsequent to metastases (especially to bones), however, the downward course is accepted to be relatively rapid. For this reason operative procedures for the alleviation of the primary lesion are undertaken with reluctance when metastases are demonstrable. A case is pre-

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sented here with metastatic carcinoma demonstrated in the bone marrow three years before death, to reopen for question the validity of extreme surgical conservatism in the presence of metastases

### CASE REPORT

A 62 year old white male entered the Cook County Hospital on September 15, 1939 because of weakness and dizziness (one week), vomiting of blood (one day), and a 20 pound weight loss (three-four months). He had been treated for peptic ulcer for 19 years, but during the last eight or nine years epigastric pain frequently associated with melena had been especially marked. His father and brother died of cancer. Noteworthy findings on examination were marked pallor, moderate emaciation, slight atrophy of the tongue papillae, a soft, inconstant apical systolic murmur, and moderate tenderness over the epigastrium and descending colon. The liver was palpable 3 to 4 cm below the costal margin.

Blood findings on admission were erythrocytes 1.34 million, hemoglobin 3.5 gm, leukocytes 16,000, neutrophils 66, lymphocytes 24, eosinophils 2, monocytes 8. The red cells showed anisocytosis, poikilocytosis, hypochromia and polychromatophilia. Ewald meal free acid 0°, combined acid 9°, lactic acid negative, blood ++. Stools (6) persistent occult blood (+ to ++++). Non-protein nitrogen 71 mg, Kahn reaction negative.

Proctoscopy (25 cm) negative. Gastroscopy pylorus and angulus normal, except for hypertrophic gastritis seen throughout stomach. Roentgen-rays increased hilar markings with calcification of lymph nodes in chest. No abnormalities in esophagus, stomach, duodenum or colon. No evidence of metastases in skull, pelvis, or long bones.

Bone marrow aspiration biopsy (sternal). "The marrow is hyperplastic and is characterized by a great number of undifferentiated cells. These cells are approximately 15-20 micra in diameter and their nuclei occupy from 70 to 80 per cent of the cell volume. The cytoplasm is deep blue in color, dense, and granular. The nuclei are lightly stained and contain a loosely woven chromatin network in which from 1-3 nucleoli are seen. These cells are frequently found in groups. Plasma cells and histiocytes are increased in number. The erythroid and granulocytic elements, as well as the megakaryocytes appear normal. Mitotic figures are not infrequent. Opinion: Invasion of the bone marrow by malignant cells."

Treatment consisted of blood transfusions (1,000 cc) and iron in addition to a bland diet. Improvement was marked and on October 18, 1939 he was discharged from the hospital.

When seen in the Out-Patient Clinic on December 6, 1939, he felt well except for occasional "gas" and sour eructations. At this time his red cell count was 4.48 million and his hemoglobin 14.4 gm. He was again seen in March 1940, but thereafter disappeared from observation.

On August 29, 1942, he reentered the hospital because of right-sided chest pain, weakness, vomiting, and tarry stools (six weeks), 40 pound weight loss (five months), epigastric pain, aggravated by meat and alcohol, and relieved by sodium bicarbonate and bland foods (two years). At this time he was pale and emaciated, had a red, smooth tongue. Breath sounds were decreased over the lower lobe of the right lung. The ribs (third to the seventh) were soft and very tender on the right side, and the seventh was freely movable. There was tenderness in the epigastrium.

Laboratory findings of interest at this time were the increased phosphatase (8.65 and 15.2 units), no Bence-Jones proteinuria, normal non-protein nitrogen, stools (3) negative for occult blood. The blood findings were erythrocytes 3.92 million, hemoglobin 11.4 gm, leukocytes 7,000, neutrophils 75, lymphocytes 25.

The roentgenographic examination of the chest cavity was non-contributory and that of the stomach was unsatisfactory because of the patient's inability to cooperate. The findings in the osseous system were "evidence of a fracture of the seventh right rib numerous oval areas of decreased bone density throughout the skull possibility of multiple myeloma should be considered. Metastatic malignancy, however, is not ruled out questionable area of decreased density in the right ischium"

Bone marrow biopsy at this time showed "the bone marrow moderately cellular. There is an occasional group composed of varying numbers of large, approximately 20  $\mu$  sized cells, having round to oval nuclei which occupy  $\frac{1}{4}$  to  $\frac{3}{4}$  of the cell volume. These cells have a grayish-blue granular cytoplasm and multiple small vacuoles. The nuclear chromatin is rather finely dispersed, and occasionally very distinct nucleoli can be seen. The number of nucleoli vary from 1 to 3. Comment: The cells above described, occurring as they do in groups and being distinctly atypical and foreign to the marrow, suggest a bone marrow replacement by metastatic neoplasm. It is interesting to note that bone marrow obtained from the patient on October 6, 1939, showed almost identical findings. The cells at present differ from those of the previous smear in that they are more vacuolated and apparently have fewer mitotic figures than previously encountered. It is difficult to conceive that a metastatic malignancy should have persisted for three years"

The course was progressively downward and on September 26, 1942, the patient died.

On postmortem examination a malignant ulcer, 5 by 6 by 0.6 cm, with well defined but undermined margins was found near the esophago-cardiac junction. Several peripancreatic and periaortic metastatic nodes, measuring up to  $3\frac{1}{2}$  cm, were seen. The liver was studded with metastatic nodules. The osseous system was diffusely infiltrated by small to large metastases. Both the primary ulcer in the stomach and the secondary lesions throughout the body were found histologically to be adenocarcinoma.

### DISCUSSION

The patient originally presented himself with the history of a peptic ulcer of 19 years' duration which had manifested itself by pain and bleeding. It is impossible to ascertain from the history when the transition from the benign to the malignant ulcer had taken place. The 20 pound weight loss antedating his admission by three or four months is the first clinical clue that significant change had taken place. It is improbable, however, that this would have been sufficient time to establish metastases. The hematological findings on this admission were compatible with acute bleeding superimposed on chronic bleeding, without casting light on the nature of the underlying lesion. The absence of free acid and the presence of blood in the gastric contents, as well as the persistent occult blood in the stools, all bespoke a malignancy. It is significant that neither gastroscopic nor roentgenographic examination revealed the lesion even though its presence at this time was confirmed by the finding of metastases. It is also noteworthy that on a bland diet and replacement therapy (iron) the blood findings became normal within a relatively short period of time. Though details in the interval are unavailable, no radical change had apparently taken place during the two and a half year period between his first hospital admission and the re-appearance of prominent symptoms, which, except those secondary to extensive bone destruction, were similar to the original. It is somewhat surprising that the blood should have remained at an adequate level in spite of episodes of bleeding and so marked a displacement of the bone marrow, and should have com-

pletely lacked the characteristics ordinarily associated with myelophthisic anemias

A feature of this case, of considerable clinical interest, is the transition from a benign to a malignant ulcer, a transition originally revealing itself clinically by extensive bleeding. At this time the lesion was so small (or so placed) as to be undiscoverable by either roentgen-ray or gastroscopy, and yet had already metastasized to bones so extensively as to be cytologically demonstrable. Of much more importance was the benign course for a two and a half year period following the demonstration of bone marrow metastasis. This raises the question whether extreme surgical conservatism is justified in the presence of demonstrable metastases, when otherwise operative intervention might be indicated for the alleviation of symptoms. It would appear, at least from this singular case, that primary surgical procedures when otherwise indicated are justified even though early metastases are demonstrable.

#### SUMMARY AND CONCLUSION

A case is presented in which metastatic carcinoma was demonstrated in the bone marrow three years before death.

It is suggested that metastases occur earlier in carcinoma than has hitherto been believed.

The attitude towards surgical intervention in the presence of metastases may bear reevaluation.

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### HEREDITARY HEMORRHAGIC TELANGIECTASIA REPORT OF TWO CASES\*

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HEREDITARY hemorrhagic telangiectasia is a rare disease, first recognized by Osler,<sup>10</sup> and is characterized by the triad of multiple telangiectases, hemorrhage, or anemia, and a history of familial occurrence. Some 500 cases occurring in over 100 families have been described.<sup>6</sup>

The characteristic lesions consist of pin-point to pea-sized telangiectases occurring most commonly in the skin and mucous membranes, but have also been described in almost every organ-system in the body—gastrointestinal tract, genitourinary system, respiratory system, and brain. These telangiectases represent dilatation of the blood vessel walls which consist of a single layer of endothelium covered with a much thinned layer of epithelium. The lesions commonly make their first appearance about the end of the first decade of life in the mucous membranes and during the third and fourth decades in the skin.

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The extreme fragility of the lesions and the time of their appearance largely determine the symptomatology of the disease. As the nasal mucous membrane is usually involved first epistaxis occurs with increasing frequency from late childhood onward. In middle life the skin and visceral lesions appear and add to the blood loss. The resulting secondary anemia may be very severe, but the hemoglobin is seldom below 50 per cent. The skin lesions occasionally disappear after a period of years, but the anemia persists. As the patient ages, the quantity of blood lost increases and a hemorrhage from the nose of 1000-1500 cc is not uncommon. The 6 per cent mortality of the disease is associated with these hemorrhages.

The hereditary factor in the disease seems to be transmitted as a simple dominant by both sexes and may affect both sexes. Teahan<sup>17</sup> has traced the disease through six generations of one family. Fitzhugh,<sup>3</sup> however, has stressed the occurrence of atavism in this disease, citing seven instances in the 212 cases reported until 1923. In one of these, two and possibly more generations were skipped. As will be indicated later, Case 1 may represent an instance of atavism.

#### CASE REPORTS

**Case 1** F L, 51 year old white male farmer, was first admitted to the medical service of the Indiana University Medical Center on March 31, 1941 with the complaints of weakness, loss of weight, abdominal pain after eating and shortness of breath.

The weakness had begun about six years previously and had progressed to the point where he was unable to work, or could scarcely carry on any of his usual activities. During this same period he had lost 25 pounds in weight.

Pain in the abdomen had begun three years before, occurring usually after meals, and was relieved by belching or soda. No hematemesis, melena, jaundice, or acholic stools had been noted. Progressively increasing dyspnea accompanied by palpitation had developed during the year previous to admission.

In the past the patient had suffered from the usual childhood diseases without complications, had influenza during the epidemic of 1918, and had typhoid fever and smallpox at the age of 21.

The family history showed his mother had died from cancer of the stomach and his father of a hemorrhage from the stomach or lungs. Two sisters and two brothers were alive and well.

The review by systems showed no difficulties aside from those listed in the present illness except some urinary frequency and nocturia four to five times. No associated hematuria, pyuria, or dysuria was present.

Physical examination revealed a pale, somewhat asthenic, middle-aged male, appearing chronically ill. The skin contained numerous telangiectases varying in size from 1 to 5 mm. These lesions were most abundant over the upper half of the face and ears, and the finger tips, but were also present in lesser numbers over the back, arms, legs, left great toe, prepuce and glans penis. The examination of the eyes was negative except for the presence of a similar lesion on the palpebral conjunctiva of the right eye. Telangiectases were also noted in the mucous membranes of the nose, throat and tongue. The heart was of normal size, rate and rhythm were regular. A systolic murmur was present at the apex. The blood pressure was 110 mm Hg systolic and 70 mm diastolic. The abdomen was moderately tender in both lower quadrants. No palpable masses were present. The liver was down two fingers' breadth. The extremities were negative except for slight pitting edema about the ankles.

Laboratory investigation revealed a normal urinalysis. Hemoglobin was 5.8 gm, red blood cells, 3,130,000, white blood cells 3,700 with a normal differential count. Platelets were 126,000 to 187,000. Average red cell diameter was 8.29 micra. Icterus index was 10. Stools were 1+ for occult blood on April 8, 1941 and April 17, 1941. The sternal bone marrow obtained by aspiration was hyperplastic with evidence of an increase in megaloblasts and was considered to resemble that seen in the pernicious anemia group.

Roentgen-ray examinations of the upper gastrointestinal tract by barium meal revealed spasticity of the duodenal bulb. No niche was present and there was displacement of the second portion of the duodenum upward and to the left. A barium enema showed a normal colon. A gall-bladder series was negative.

The patient was discharged on April 19, 1941, undiagnosed, and was instructed to return to the out-patient clinic in two months. The patient failed to return at the specified time and was not seen again until October 7, 1942. At that time he stated that for six months after leaving the hospital he felt fairly well and had been able to carry on his work but then had become progressively weaker, until at this time taking only a few steps completely exhausted him.

The remainder of his complaints were essentially the same as on his previous admission except that his urinary frequency was now accompanied by some dysuria.

Physical examination revealed little change except a loss of weight from 111 to 105 pounds.

Laboratory examination at this time showed a normal urinalysis. Hemoglobin was 6.5 gm, red blood count 3,710,000, white blood count 6,650 with a normal differential count. Blood volume index was 0.84, color index 0.58 and saturation index 0.69. Platelets were 130,200. Bleeding time was 2½ minutes, clotting time 4½ minutes, with normal clot retraction. Icterus index was 5. Van den Bergh direct reaction was negative, indirect less than 0.1 mg per cent bilirubin. Stools were 4+ for occult blood. Gastric analysis by the alcohol-histamine technic revealed adequate free HCl and was positive for blood in all fractions. Serologic reactions were negative. Phenolsulfonphthalein excretion was 30 per cent in 15 minutes and 21 per cent in 30 minutes. Sternal bone marrow showed a very mild hyperplasia.

This time the nature of the patient's condition was recognized and upon further questioning it was found that the patient had suffered from nose bleeds since the age of six years, although these had not become frequent until about the age of 12-14. The telangiectases on his face had first appeared at about the age of 40, and those on his fingers had followed a few years later. These lesions were known to bleed profusely on very slight trauma. No family history of similar lesions could be obtained among the patient's ancestors or among his own children. In spite of the fact that his father died of hemorrhage, the patient did not believe that he suffered from a similar condition.

Although it was felt that the blood in the stools could be explained by that observed in the posterior nasopharynx, a more thorough examination of the gastrointestinal and respiratory tracts was made. Telangiectases were seen in the mucous membranes of the nose and nasopharynx, uvula, mouth and tongue. Similar lesions were observed in the trachea, two in the right main stem bronchus, but none in the esophagus or portion of the stomach which could be observed with the esophagoscope. Proctoscopic examination revealed a small, reddened area approximately 5 mm in diameter about 4 cm in on the anterior wall which resembled the lesions seen in the skin.

A biopsy of one of the finger lesions showed very marked telangiectasia in the capillaries of the dermis.

The patient was placed on ferrous sulphate gr 5 three times a day, and in nine days the maximum reticulocyte response of 34 per cent was reached. The hemo-

globin rose to 10 gm and the red blood count to 4,980,000 on October 23, 1942. The patient was given one transfusion of 500 cc of blood on October 26, 1942, and on discharge the hemoglobin was 12.5 gm.

*Case 2* A S, 70 year old white laborer, has had six admissions to the Indiana University Medical Center because of severe epistaxis and associated anemia. When first seen on March 24, 1936 he was having small nose-bleeds every three to four days and severe nose-bleeds (500 cc or more) every five to six months. Since that time his severe epistaxis has become more frequent until he has now become a chronic invalid.

The patient's history dates back to 1874 when at the age of three he was butted by a ram and his nose broken. This was followed by severe epistaxis and throughout childhood epistaxis was frequent. During young adulthood he had little difficulty and was able to work as a manual laborer. In 1917, at the age of 45, he had influenza and following this he again began to have epistaxis. Also about this time he first remembers the presence of numerous telangiectases on his face which would bleed profusely if cut while shaving. In 1920 he was treated with radium at the Mayo Clinic, and between that time and 1936 he had radium four more times and cold cautery to the nasal septum numerous times. In 1934 he contracted syphilis and received four months' treatment of alternate arsenic and bismuth injections. Previous to his second admission to the hospital on December 18, 1938, he complained of hematuria and profuse hemorrhage from a ruptured telangiectasis on his face. In 1940 he had a small hemorrhage from his left eye.

Concerning his family history, he stated that his mother had telangiectases and that a daughter age 43, had suffered from frequent epistaxes since childhood and had telangiectases on the face.

Physical examination on his last admission, September 4, 1942, showed a pale, undernourished elderly white male. Telangiectases were present in the skin of the face, scalp, ears, chest, back, legs, glans penis, palms of the hands, sides of the fingers and toes, being most abundant over the face, ears, and fingers. Similar lesions were seen in the mucous membranes of the mouth, palpebral conjunctiva, and nose. The anterior half of the nasal septum was absent and three small arteries were once seen in the floor of the nose. Bilateral cataracts were present and the fundus could not be seen, but a note made by the resident in Ophthalmology in 1939 stated that there was an unusual pigment distribution with a piling up of pigment just superior to the left disk, resembling an old hemorrhage. Examination of the lung fields was negative. The heart size was within normal limits, rate 68, and rhythm regular. A rough systolic murmur was present at the apex but not transmitted. Blood pressure was 105 mm Hg systolic and 60 mm diastolic. The abdomen contained no masses or areas of tenderness. The liver and spleen were not palpable.

Direct laryngoscopy and bronchoscopy revealed a 3 mm telangiectasis on the apex of the epiglottis, similar lesions on the left side of the trachea about the level of the fourth ring, and a minute spider lesion at the anterior extremity of the carina. The main stem bronchi and all bronchial orifices contained no lesions. Esophagoscopy was negative. Sigmoidoscopy revealed a vascular spider-like arrangement 12 cm up in the left wall, 0.5 cm above this network the channel was dilated to a size two to three times greater than that of the channels in the network.

During the seven years the patient has been followed, the hemoglobin has ranged from 3.2 to 10.5 gm, but has usually been between 5.5 and 7.5 gm with red cell counts between 2.5 and 3 million. White blood cell and differential counts have been normal. Platelet counts were 320,000 to 370,000. Bleeding time was two minutes, clotting time five minutes and clot retraction complete in 90 minutes. Urinalyses have shown occasional red blood cells at infrequent intervals. Serologic reactions have been negative on each admission.

On his first and fifth admissions the nasal septum was cauterized with silver

nitrate, but in most instances his epistaxis has been so profuse that it has been impossible to locate the bleeding points. The patient has received 40 blood transfusions since being followed at the Medical Center, 10 of these being given during his last admission. During this admission from September 4, 1942 to January 25, 1943, he had 10 major episodes of epistaxis ranging in quantity from 100 to 850 cc. His hemoglobin on this admission was 5.5 gm. Following nine transfusions it reached 10.5 gm on December 3, 1942. The patient was unable to procure more donors and on discharge it had again fallen to 5.8 gm. Between episodes of severe epistaxis there was almost always a constant oozing of blood so that it could always be seen in the posterior nasopharynx.

*Comment* As only one brother and the eldest son of the first patient could be examined, and the source of the father's hemorrhage cannot be determined we are unable to decide whether this represents an instance of atavism. The two members of the family examined showed no telangiectases and the patient stated that none of his family suffered from frequent epistaxis or skin lesions similar to his. As the clinical picture of the disease is sufficiently clear, it may mean that this is another instance of atavism to be added to those already described, or it may be that as his children grow older, one or more of them may develop evidence of the disease.

Although lesions in the colon similar to those seen in these two cases have been described before,<sup>1</sup> the incidence of telangiectases in the remainder of the gastrointestinal tract is probably not as great as a cursory review of the literature would seem to indicate. Too many of these reports<sup>7,8</sup> base their conclusions on the finding of occult blood in the stools. These conclusions hardly seem justified when it is remembered that varying amounts of blood may almost always be found in the nasopharynx of these patients and would certainly lead to a positive test for occult blood in the stools.

Only three observers have reported cases in which the presence of telangiectases in the stomach has actually been proved. Osler<sup>10</sup> in his original communication described one case at autopsy, but this man died of carcinoma of the stomach which might cast some doubt on the nature of the telangiectases. Boston<sup>2</sup> described two cases, in one of whom the lesions were seen at operation performed because of profuse gastric hemorrhage, and in the other the lesions were found at autopsy following repeated gastric hemorrhages. The sister of the second case also died of gastric hemorrhage. Both cases had the skin lesions and a positive family history. Renshaw<sup>11</sup> reported a case in which eight lesions were seen in the mucosa of the antrum, two on the angularis, and four on the lesser curvature of the stomach with the gastroscope. In the two cases reported here, no telangiectases were seen in the esophagus, or the portion of the stomach seen by the esophagoscope. Both cases did have symptoms somewhat suggestive of peptic ulcer, however, and in case 2 roentgen-ray examination was reported as suggestive of duodenal ulcer. Whether this lesion was associated with telangiectases remains to be proved.

Fitzhugh<sup>4</sup> described four cases of hereditary hemorrhagic telangiectasia, all of whom had hepatomegaly, splenomegaly, increasing intolerance to blood transfusions, and all were of blood type O. These conditions were not present in our cases, nor have they been noted in many other cases.<sup>12</sup> A possible explanation for this is advanced by Williams and Snell<sup>14</sup>. They described six cases of telangiectasia associated with liver disease, one of which was hereditary, and

advanced the theory that the hereditary type of disease is dominant and the hepatic recessive

Although our second patient complained of gross hematuria on one occasion, during his numerous hospitalizations he showed only microscopic hematuria and this rarely. This apparently is characteristic of the disease as no cases with hematuria have been described in the American literature. Hereditary telangiectasia, however, possibly offers an explanation for some of the cases of so-called "essential hematuria." Blum<sup>1</sup> described a family in which the mother had severe nose bleeds, two of her children had hematuria, two had nose bleeds, and one was normal. Another of his patients, aged 53, had hematuria twice, then melena three times. No telangiectases were present on the skin, but he stated they had been present at about the age of 40 and then disappeared. Foggie<sup>5</sup> reported one case of hematuria in a patient in whom the skin lesions were present. There was a history of epistaxis on the mother's side of the family and the mother also probably suffered from hematuria. Keller<sup>6</sup> recorded the case of a child, age 9, who had one episode of hematuria, two of epistaxis, and another of hematuria within a year. Telangiectases were present on the nasal, oral, and pharyngeal mucous membranes, but none on the skin. There was a family history of epistaxis and hematuria extending back three generations. He noted that epistaxis and hematuria never occurred at the same time and expressed the belief that some families will show hematuria and other skin lesions, and that hematuria is the most common lesion in childhood and skin lesions the more common in the adult.

Although various forms of treatment have been advocated, none seems to be satisfactory. Cauterization of the bleeding points and radium packs have been advocated to control the epistaxis. The application of these treatments in Case 2 has resulted in necrosis of the septal cartilage and his bleeding continued, especially from small arteries coming up through the floor of the nose. It has also been suggested that if the anemia is adequately controlled the telangiectases will regress. This has not been our experience in these cases, and it has been impossible to maintain an adequate hemoglobin level except by very frequent transfusions. Treatment has, therefore, been symptomatic—using pressure packing to control hemorrhage, and ferrous sulphate for the anemia. The use of thromboplastic substances has seemed to reduce the frequency of hemorrhages, although there would seem to be no physiologic basis for this improvement.

#### SUMMARY

- 1 Two cases of hereditary hemorrhagic telangiectasia have been presented
- 2 Both cases have hemoglobin levels lower than those usually described in this disease, lesions in the skin, mucous membranes, upper respiratory tree, and colon. Case 2 had microscopic hematuria on rare occasions
- 3 Case 1 may represent an additional instance of atavism in this disease but further proof is required before this conclusion can be reached
- 4 Both cases have proved very refractory to the recommended forms of treatment

#### CONCLUSIONS

In cases of recurrent epistaxis or chronic secondary anemia for which no cause can be ascertained, hereditary hemorrhagic telangiectasis should be con-



sidered and a search made for the characteristic lesions in the nasal, oral and pharyngeal mucous membranes. The presence of telangiectases in the skin and a family history of similar lesions or frequent epistaxis complete the diagnosis. Treatment of this condition at present seems to have little effect on the course of the disease.

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### TORULA HISTOLYTICA (CRYPTOCOCCUS HOMINIS) MENINGITIS CASE REPORT AND THERAPEUTIC EXPERIMENTS\*

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APPROXIMATELY 80 cases of *Torula histolytica* meningitis have been reported since 1861, when, according to Freeman,<sup>1</sup> Zenker recorded what was probably the first case. Less than half of the cases have been recognized before

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death.<sup>2</sup> It has been mistaken for tuberculous meningitis, brain abscess, brain tumor, encephalitis, lymphocytic choriomeningitis, and dementia paralytica. *Torula histolytica* is widely distributed in nature having been isolated from wasp nests, stems of grasses and plants, bodies of insects, canned butter and milk.<sup>3, 4</sup> Lesions such as localized dorsolumbar abscess,<sup>5</sup> pelvic and inguinal abscess,<sup>6</sup> and nasopharyngeal ulcers<sup>7</sup> have been caused by *Torula histolytica*. Some<sup>8, 9</sup> are inclined to regard the injury to the body as resulting from mechanical pressure and a lytic secretion. Neither endotoxin nor exotoxin has been satisfactorily demonstrated. The body's defenses seem to be tissue immunity and local phagocytosis by cells of the reticuloendothelial system. In the humoral system only weak agglutinins have been demonstrated.<sup>8, 10, 11</sup> It is not known why the human body is not more frequently invaded by this widely disseminated yeast-like organism, but no doubt, as in bacterial infections, disease depends on the virulence of the invader as opposed to the resistance of the host. Rabinowitsch is reported by Rappaport and Kaplan<sup>8</sup> to have found only eight of 40 strains isolated from various sources in nature to be pathogenic.

Most cases occur in the third and fourth decades and twice as frequently in males as in females. *Torula histolytica* meningitis has been considered to be invariably fatal, although recently Marshall and Teed,<sup>12</sup> in a preliminary report, present a case of apparent cure from sulfadiazine. However, not enough time has elapsed in this case to be sure, for the disease has been known to last as long as five years with spontaneous remissions only to end fatally. Gill<sup>7</sup> reported a case of orbital abscess with involvement of the ethmoid sinuses, the antrum and the hard palate. On one occasion *Torulae* were cultured from the blood. The patient recovered and is known to have been well for seven years.

The reporting of our case is felt to be justified since two therapeutic experiments were carried out, complete pathologic study made, the therapeutic effect of sulfadiazine on experimental infection in mice studied and the effect of sulfadiazine and penicillin on the organism in vitro observed.

#### CASE REPORT

H. H., a 50 year old white man, was admitted to the Samaritan Hospital January 23, 1943 complaining of headache of five days' duration. It was located in the frontal region and radiated to both ears. The pain was stabbing sharp and intermittent. It became progressively worse. He had not been feeling well for the previous eight months, tiring easily and suffering from nervous tension. A physician, whom he had consulted, told him he was having a "nervous breakdown" and advised complete rest. However, he continued work as a hairdresser until shortly before admission to the Hospital.

In 1939 a large portion of his stomach was resected for primary carcinoma and a cholecystectomy for biliary calculi was performed at the same time. A recent checkup at the Lahey Clinic, where the operation had been done, failed to show the presence of malignant disease. During World War I he spent two years in a Russian prison camp as a German prisoner, but had lived in the United States for the 20 years preceding admission.

Special inquiry and family history were noncontributory.

Physical examination showed the patient to be a middle-aged apparently healthy man, lying comfortably in bed. Nutrition and development were good. The temperature on admission was 102.4° F rectally, pulse 96, respirations 20 and blood pressure 110 mm Hg systolic and 60 mm Hg diastolic. The positive findings were

(1) marked stiffness of the neck, (2) bilaterally positive Kernig sign, (3) inconstant Babinski and Chaddock reflexes in left foot, (4) slight blurring of the optic disk, (5) hyperactive reflexes

*Laboratory Data* On the day of admission the spinal fluid pressure was normal. The fluid contained 75 mg of protein per 100 c.c. and had a reported cell count of 64 per cu. mm., of which 53 per cent were said to be lymphocytes and 47 per cent polymorphonuclears, but *Torulae* were mistaken for lymphocytes in this count. The blood contained 9,400 leukocytes per cu. mm. of which there were 85 per cent polymorphonuclears, 10 per cent lymphocytes, 2 per cent eosinophiles, 2 per cent basophiles and 1 per cent monocytes. Examination of the urine showed no abnormality. The complement fixation test for syphilis and the agglutination test for the presence of typhoid and paratyphoid antibodies made on the blood were negative. Roentgenograms of the chest showed only slight accentuation of the normal lung markings.

Several days after admission yeast-like organisms, at first thought to be contaminants, were cultivated from the spinal fluid. Two subsequent blood cultures and a second spinal fluid culture all yielded a heavy growth of the same organism, which was tentatively identified as *Torula histolytica* as it was non-sporulating, had no hyphae, was Gram-positive in young cultures and Gram-negative in older cultures. Later it was shown to be non-pathogenic to guinea pigs after two months and pathogenic to mice in 12 days. A sub-culture submitted to the National Institute of Health was identified by Dr. C. W. Emmons as "*Cryptococcus hominis*."

During the course of the illness the blood contained between 5,900 and 9,450 leukocytes per cu. mm. with no significant changes in the differential count. The blood contained 114 mg of glucose per 100 c.c. when the patient was fasting. This determination was made with the thought that the *Torulae* might possibly act upon the glucose in the blood to cause hypoglycemia, although it was realized that under ordinary circumstances the organism does not ferment this sugar. Two days after admission the spinal fluid still showed no pressure changes. The fluid was reported to contain 38 cells per cu. mm., of which 63 per cent were polymorphonuclears and 37 per cent lymphocytes, but here again *Torulae* and lymphocytes were not differentiated. The spinal fluid contained 34 mg of glucose and 75 mg of protein per 100 c.c. The sedimentation of erythrocytes (Wintrobe method) was 10 mm. in one hour.

*Treatment* Two blood transfusions, iodides orally and intravenously, and sulfadiazine (discontinued after four days as leukopenia threatened) caused no appreciable improvement. Gentian violet intravenously and thymol intramuscularly had been suggested for monilia infection of the lungs,<sup>13</sup> but to our knowledge had never been used in torulosis. Gomez-Vega<sup>14</sup> showed that gentian violet in 1/100,000 solution would inhibit the growth of *Torulae* in vitro. Accordingly 300 mg of gentian violet in 5 per cent solution in distilled water were given intravenously daily for seven days. Since Myers<sup>15</sup> had found evidence of therapeutic activity of thymol in actinomycosis, we later used 180 mg of this substance dissolved in 3 c.c. of olive oil intramuscularly daily for seven days. No benefit was noted following the use of either of these substances. Penicillin was unobtainable in sufficient quantity for adequate therapy.

Neal and Shapiro<sup>11</sup> found *Torula histolytica* meningitis refractory to the following treatments: autogenous vaccine, colloidal silver intrathecally, Fowler's solution orally, iodides orally and intrathecally and serum intrathecally, from rabbits which had received intravenous injections of *Torulae*. These authors found slight to no inhibition of growth in vitro in the presence of sodium iodide 1/500, sodium salicylate 1/500, colloidal silver 1/600, magnesium sulphate 1/500, rochelle salts 1/500, tricresol 1/1000 and quinine in saturated solution. A 1/10,000 solution of acriflavin caused well marked inhibition of growth and 1/5000 complete inhibition. Warvi and Rawson<sup>16</sup> suggested using acriflavin intrathecally in 1/10,000 solution. This was not done in our case since the infection was not confined to the meninges, but was

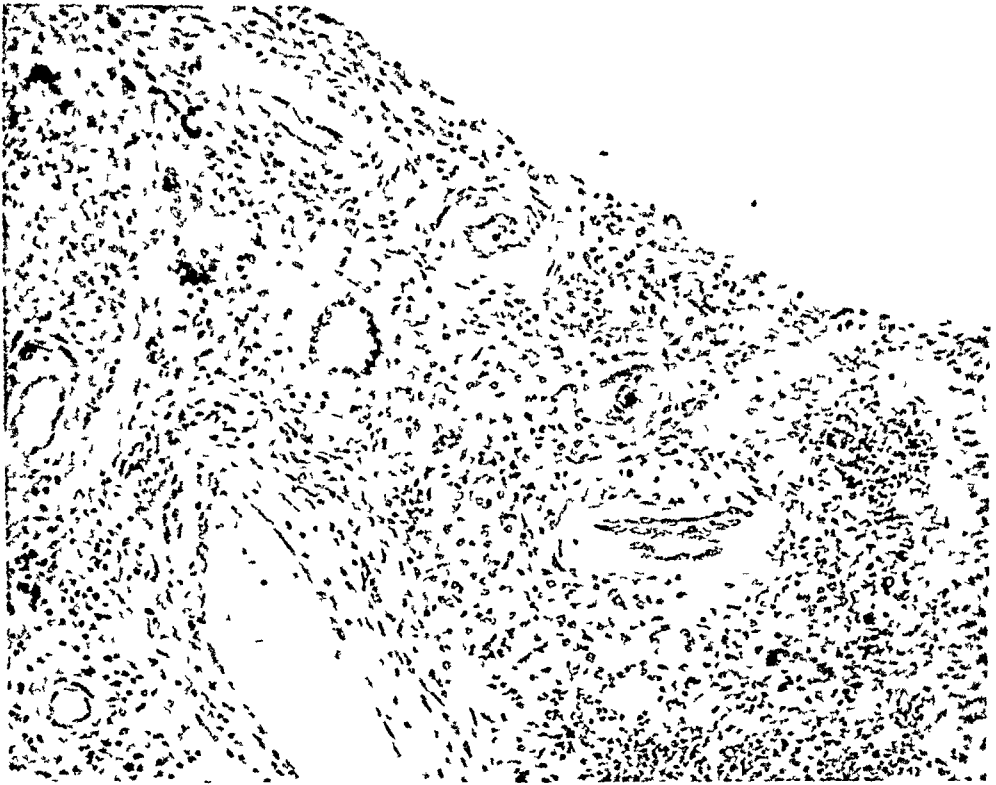


FIG 1 Leptomeninges of upper cervical spinal cord showing inflammatory reaction. Lymphocytes, epithelioid cells, vacuolated giant cells and necrosis of exudate are seen.

generalized. Gentian violet was chosen rather than acriflavine because of its greater affinity for Gram-positive organisms.<sup>17</sup>

*Course.* Headache became more severe, hearing diminished, vision weakened and anorexia, loss of weight and weakness developed. At the end the patient was confused and bedridden and died in a convulsion 46 days after the onset of headache.



FIG 2 Vacuolated giant cell containing *Torulae* in leptomeninges.

*Autopsy* Autopsy was performed six hours after death. The brain, spinal cord and kidneys were the only organs which showed infection by *Torula*. Incidental findings included a diaphragmatic hernia on the left side and calcified mesenteric lymph nodes, as well as evidence of ancient, partial gastrectomy, gastrojejunostomy and cholecystectomy.

*Central Nervous System* The dura mater was not tense and was of normal thickness. No increase in the amount of subdural fluid was noted. The leptomeninges covering the vertex, lateral, anterior and posterior aspects of the brain, were of normal thickness but there was a slightly increased amount of clear subarachnoid fluid. The blood vessels were slightly congested. The leptomeninges of



FIG 3 Kidney showing multiple, miliary abscesses and intense congestion

the under surface of the brain, particularly in the region of the optic chiasm, the anterior surface of the pons, the entire medulla and the under surface of the cerebellum, were slightly thickened and opaque due to the presence of a grayish exudate, which appeared to be located chiefly below the membranes. In places, however, some jelly-like, grayish-yellow material was found on the surface. The cranial nerves and the portion of spinal cord visible through the foramen magnum were surrounded by similar exudate. A pressure cone was not present. The brain, which was symmetrical, weighed 1510 gm. After hardening in formaldehyde solution further examination showed very slight dilatation of the lateral ventricles. The choroid plexuses were opaque and matted, while the lining of the ventricles was rough in places. A segment of the lower thoracic and lumbar portions of the spinal cord was negative on inspection. *Histologic examination* revealed the leptomeninges of basal portions of the brain and of all portions of the spinal cord to be greatly thickened as

a result of an inflammatory reaction characterized by the presence of large numbers of closely-placed, elongated cells with oval nuclei resembling epithelioid cells, lymphocytes and large numbers of giant cells (figure 1). In some places there was extensive necrosis of the inflammatory exudate. Large numbers of *Torulae* were found outside of and within giant cells (figure 2). The cranial nerves, the large nerves of the spinal cord and the meninges of the spinal cord supported similar inflammatory exudate. The reaction in the meninges was found to accompany branches of the meningeal vessels which entered the brain. The ependyma and choroid plexuses supported large amounts of exudate similar to that described in the meninges but in addition many polymorphonuclear leukocytes were present. In places the ependyma was very irregular in contour and sometimes broken. Beneath some of the breaks

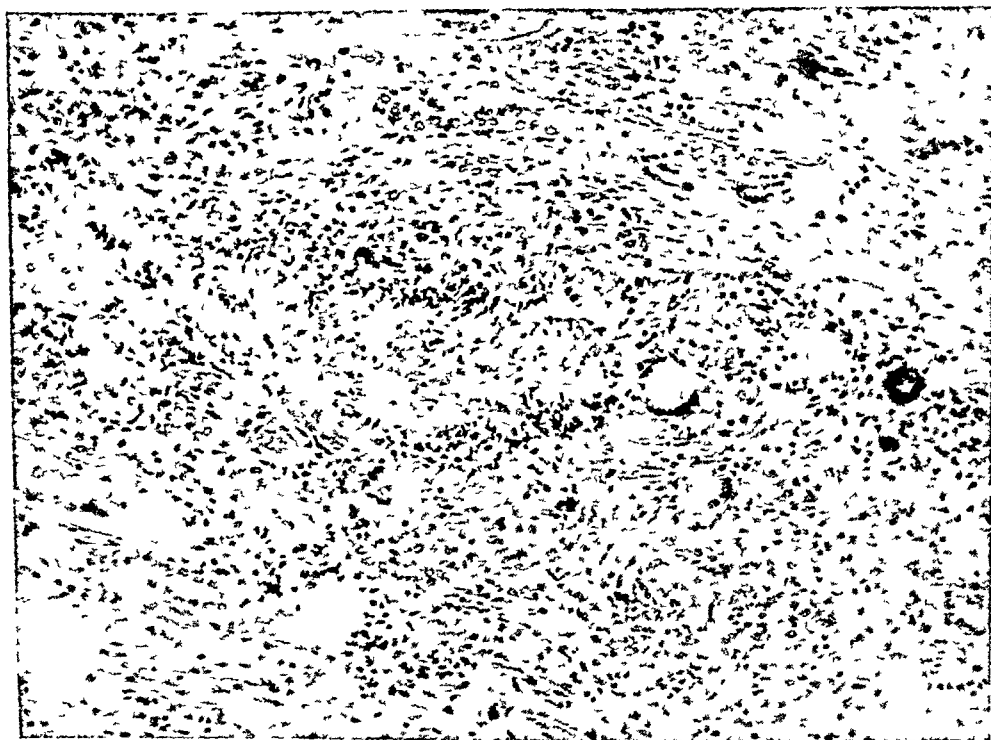


FIG 4 Lesion in kidney resembling a miliary tubercle. Vacuolated giant cells containing *Torulae* are present.

there was proliferation of glial tissue, which extruded into the ventricle and accounted for the roughness described grossly. The brain substance and the substance of the spinal cord revealed nothing of note, except a few poorly-developed collars of lymphocytes around some of the vessels near the ependyma. Preparations of fluid from the lateral ventricles showed budding *Torulae*.

**Kidneys** The right kidney weighed 230 gm, was very large, quite firm and dark purple. The capsule was easily removed and exposed a somewhat lobulated surface broken by the presence of numerous, slightly elevated, round, grayish lesions averaging 0.2 cm in diameter. Similar lesions were found scattered throughout the cortex and medulla (figure 3). In places there were grayish streaks in the medullary portions. The pelvis was negative except for a few congested blood vessels. The left kidney weighed 250 gm and was similar to its fellow. *Histologic examination* revealed numerous focal lesions characterized by the presence of giant cells and epi-

thelioid cells. The lesions were about the size of miliary tubercles and irregular in shape but tended to be elliptical. Some of the lesions simulated miliary tubercles in that they presented caseous centers surrounded by palisaded epithelioid cells. Peripheral to the palisaded cells were many unoriented epithelioid cells, some monocytes and large giant cells (figure 4). Some of the lesions contained large numbers of multinucleated giant cells but no evidence of necrosis. Torulae were found in large numbers within and outside of giant cells and occasionally within spaces lined by endothelium believed to be lymph vessels (figure 4).

Cultures at autopsy, taken from the vertex and base of the brain, the kidneys and blood, yielded *Torula histolytica*.

### EXPERIMENTS

Sodium sulfadiazine was added to a nutrient broth culture medium to give a concentration of 1 per cent, 0.1 per cent and 0.01 per cent. Three tubes of each concentration and three tubes of nutrient broth, each containing 1500 Florey units of penicillin, were inoculated with *Torula histolytica* and incubated aerobically at 36° C. Growth of the organism was abundant in each of the tubes at the end of four days. It would appear that neither sodium sulfadiazine nor penicillin inhibits the growth of *Torula histolytica* in vitro.

To determine whether or not sulfadiazine has any effect against *Torulae* in vivo, the following experiment was performed. Twenty mice were injected intraperitoneally with 1 c.c. of a 1 per cent suspension of *Torula histolytica* (approximately 100 million organisms) and left untreated. Another group of 20 were similarly injected, but, in addition, were given 0.4 c.c. of a 5 per cent solution of sodium sulfadiazine (20 mg.) subcutaneously daily. This dose was chosen after preliminary trials demonstrated that mice could tolerate this amount indefinitely. Bodansky<sup>18</sup> determined the m.l.d. for mice to be 1.5 gm. per kilogram of weight and Feinstone et al.<sup>19</sup> found the m.l.d. to be 1.2 gm. The dose we used was equivalent to 1 gm. per kilogram. The survival period of the untreated and treated groups is shown in table 1.

TABLE I

#### Untreated

No. of Mice	Days Survived	Mouse days
5	9	45
5	12	60
1	13	13
4	14	56
5	15	75
<hr/> 20	<hr/>	<hr/> 249

$$\text{Average} = \frac{249}{20} = 12.45 \text{ days}$$

#### Treated

No. of Mice	Days Survived	Mouse days
8	3	24
2	4	8
5	5	25
3	6	18
2	7	14
<hr/> 20	<hr/>	<hr/> 89

$$\text{Average} = \frac{89}{20} = 4.45 \text{ days}$$

Because the dose of sodium sulfadiazine was so large, the experiments were repeated using smaller doses. Fifteen mice were injected as before with *Torulae* and left untreated. Another 15 were similarly injected and treated with 0.1 c.c. of a 2.5 per cent solution (2.5 mg.) of sodium sulfadiazine subcutaneously daily. A third group of 15 were likewise injected with *Torulae* but treated with 0.2 c.c. (5 mg.) of the sodium sulfadiazine solution subcutaneously daily. These amounts of sulfadiazine are equivalent to 0.1 to 0.2 gm. respectively per kilogram of body weight, a dose corresponding to that used clinically. The survival periods of these groups are shown in table 2.

TABLE II  
Untreated

No. of Mice	Days Survived	Mouse days
4	12	48
4	14	56
1	16	16
2	17	34
1	19	19
2	20	20
(1)*	—	—
<hr/> 14	<hr/>	<hr/> 193

$$\text{Average} = \frac{193}{14} = 13.8 \text{ days}$$

Treated with 0.1 c.c. of 2.5% solution of sodium sulfadiazine daily

No. of Mice	Days Survived	Mouse days
1	8	8
1	9	9
1	10	10
2	12	24
3	13	39
3	14	42
1	15	15
1	17	17
1	23	23
(1)*	—	—
<hr/> 14	<hr/>	<hr/> 187

$$\text{Average} = \frac{187}{14} = 13.35 \text{ days}$$

Treated with 0.2 c.c. of 2.5% solution of sodium sulfadiazine daily

No. of Mice	Days Survived	Mouse days
1	8	8
1	9	9
3	10	30
2	11	22
2	13	26
2	14	28
1	15	15
1	16	16
1	19	19
(1)*	—	—
<hr/> 14	<hr/>	<hr/> 173

$$\text{Average} = \frac{173}{14} = 12.35 \text{ days}$$

\* One mouse in each group was still alive at the end of four weeks when the experiment was discontinued.



## DISCUSSION

From these experiments, in vivo and in vitro, it appears that sodium sulfadiazine has no demonstrable effect on *Torulae*. Penicillin does not appear to inhibit the growth of the organism in vitro. No known treatment is of proved value in torulosis. The organism is vigorous and resistant while the humoral defenses are apparently weak. Possibly one of the newly discovered antibiotics may be shown to be effective.

## SUMMARY

1 A case of *Torula histolytica* meningitis with postmortem findings has been presented.

2 Neither gentian violet nor thymol had any therapeutic value in this infection.

3 Experiments in vitro failed to demonstrate any growth-inhibiting effect of sodium sulfadiazine or penicillin on *Torulae*.

4 Experiments failed to show any therapeutic value of sodium sulfadiazine in experimental mouse infection.

The authors are indebted to Dr. Frances Hayward Smith for considerable assistance with the experiments and to Dr. O. W. Barlow of Winthrop Chemical Co., Inc. for supplying penicillin and thymol in oil.

## ADDENDUM

Since this paper was submitted Dawson et al.\* have included the *Cryptococcus hominis* in a list of organisms susceptible to penicillin. One of us (S. H. J.), now at the Lahey Clinic, with the assistance of Mr. H. J. Perkin, director of the clinic laboratory, confirmed the previous conclusion that our strain is not susceptible to penicillin. In tubes of nutrient broth containing respectively 10,000, 5,000, and 2,000 units of penicillin, growth was not grossly inhibited. Mice to which the organism proved fatal lived an average of 14.5 days, while mice treated with 80 units of penicillin approximately every three hours day and night for 12 days lived an average of 14.8 days, which is not significantly different.

Untreated		
No. of Mice	Days Survived	Mouse days
1	8	8
1	10	10
1	11	11
1	12	12
3	14	42
1	15	15
1	16	16
2	17	34
1	19	19
1	22	22
2 (living after 28 days)	—	—
15	—	189

$$\text{Average} = \frac{189}{13} = 14.5 \text{ days}$$

\* DAWSON, M. H., HOBBY, G. L., MCFYER, K., and CHAFFE, E. Penicillin as a chemotherapeutic agent, *Ann. Int. Med.*, 1943, 19, 707-717.

No of Mice	Treated	Mouse days
2	9	18
2	12	24
3	13	39
1	16	16
3	17	51
1	19	19
1	25	25
2 (living after 28 days)	—	—
15	—	192

$$\text{Average} = \frac{192}{13} = 14.8 \text{ days}$$

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## EDITORIAL

### THE ETIOLOGIC AGENT OF GRANULOMA INGUINALE

GRANULOMA inguinale (granuloma venereum) is a form of venereal infection which is common and widespread in the tropics, including the West Indies. Although rarely recognized in the northern United States, many cases have been observed in the southern states, particularly among the negroes. The lesions are usually limited to the genital regions and start as small vesicles or papules on the penis or labia minora, slowly spreading over the adjacent skin and mucous membranes. These lesions rupture or become excoriated, producing foul ulcerations covered with granulation tissue which may become exuberant and fungating. The lesions may be very mutilating, and they show little tendency to heal spontaneously, but except when modified by secondary infection they rarely involve the deep tissues, affect the lymph nodes, or impair the general health.

The most characteristic feature of the lesions microscopically is the presence of many mononuclear phagocytes containing inclusions which were first described by Donovan in 1905 and have since been known as Donovan bodies. These are small ovoid or short rod shaped bodies surrounded by a thick halo, or capsule, and are present often in large numbers in or around vacuolated areas in the phagocytes. They are Gram negative, but stain readily with Giemsa's or Wright's stain. Similar unencapsulated bodies are also found extracellularly in the lesions, and these may show bizarre variations in structure.

These bodies were regarded at first as protozoa, related to *Leishmania*. This view received some apparent confirmation from the fact that antimony compounds are therapeutically effective in this disease. Many attempts were made to cultivate organisms from the lesions, and in a number of cases cultures yielded bacteria related to the Friedlander bacillus, which have been designated *Klebsiella granulomatis*. Attempts to reproduce the disease with such cultures in animals and in human volunteers, however, were uniformly unsuccessful. More careful subsequent studies, notably by Johns and Gage<sup>1</sup> and by DeMonbreun and Goodpasture,<sup>2</sup> confirmed the constant presence and probable significance of the Donovan bodies, but no growth could be obtained on any ordinary culture medium, nor could lesions be produced in the usual laboratory animals or in the chorioallantoic membrane of the chick embryo. They used material aspirated from early unruptured lesions ("pseudobubos") which was rich in Donovan bodies but contained no other demonstrable organisms. Greenblatt, Dienst, et al.<sup>3</sup> confirmed these

<sup>1</sup> JOHNS, F. M., and GAGE, I. M. Granuloma inguinale and cultural studies of Donovan bodies, *Internat. Clin.*, 1924, iv, 15.

<sup>2</sup> DEMONBREUN, W. A., and GOODPASTURE, E. W. Etiological studies of granuloma inguinale, *South Med. J.*, 1931, xxiv, 588.

<sup>3</sup> GREENBLATT, R. B., DIENST, R. B., PUND, E. R., and TORPIN, R. Experimental and clinical granuloma inguinale, *Jr. Am. Med. Assoc.*, 1939, cxiii, 1109.

observations, and with such material successfully reproduced the disease in four human volunteers

More recently Anderson<sup>4</sup> and Anderson, DeMonbreun and Goodpasture<sup>5</sup> have reported the successful cultivation of the organism in the yolk of developing chick embryos from three human cases of granuloma inguinale. Inoculation of uncontaminated material into the yolk of developing embryos between the fourth and eighth day of incubation resulted in infection, the yolk removed four days after inoculation containing large numbers of morphologically typical encapsulated Donovan bodies. These were carried on indefinitely in serial cultures. When inoculated into older embryos, non-encapsulated forms with variable morphology were observed, like the extracellular forms in human lesions. The bodies also grew within the epithelial cells of the yolk sac, but did not invade any other tissues of the embryo.

Inoculation of laboratory animals, including rhesus monkeys, with such cultures produced no lesions. Attempts to produce the disease with these cultures in human volunteers have not been reported.

The organisms were cultivated in vitro in the fluid yolk aspirated from fertile eggs between the fourth and eighth day of incubation, viable embryo heart being necessary also for the first few transfers. They also grew in the water of condensation of agar slants containing 50 per cent of such yolk. They would not grow on coagulated yolk, or in the yolk of nonfertilized eggs. They evidently require some substances liberated by growing cells, although they are not obligate intracellular parasites. The nature of these substances is not known.

Anderson et al. regard the organism as a bacterium, bacillary in type, entirely unrelated to the Friedlander group, and differing from ordinary bacteria in its peculiar growth requirements. They have proposed for it the name *Donovania granulomatis*.

Anderson, Goodpasture and DeMonbreun<sup>6</sup> also studied the antigenic properties of the organisms. Heavy suspensions of organisms were obtained by centrifugalizing fluid yolk from infected eggs. The organisms were washed as free as possible from egg yolk and were killed by heating at 60° C. Intracutaneous injections of suitable dilutions of the suspended organisms caused typical hypersensitive reactions in six cases of granuloma inguinale, whereas no reactions occurred in four control cases. Less marked positive reactions were also obtained in these cases of granuloma inguinale with a filtrate of infected yolk, but not with filtrate of normal yolk.

Precipitin and complement fixation reactions were also carried out. These investigators noted that when the organisms were cultured serially in

<sup>4</sup> ANDERSON, K. Cultivation from granuloma inguinale of microorganism having characteristics of Donovan bodies in yolk sac of chick embryos, *Science*, 1943, xcvi, 560.

<sup>5</sup> ANDERSON, K., DEMONBREUN, W. A., and GOODPASTURE, E. W. An etiologic consideration of *Donovania granulomatis* cultivated from granuloma inguinale (three cases) in embryonic egg yolk, *Jr Exper Med*, 1945, lxxxi, 25.

<sup>6</sup> ANDERSON, K., GOODPASTURE, E. W., and DEMONBREUN, W. A. Immunologic relationship of *Donovania granulomatis* to granuloma inguinale, *Jr Exper Med*, 1945, lxxxi, 41.

embryos inoculated on the fifth day of incubation, the yolk gradually acquired aropy mucoid consistence, and the organisms showed capsules which were no longer compact, but appeared shredded and disintegrated, apparently disseminating into the surrounding medium. This mucoid material could be dissolved readily in dilute alkali and reprecipitated by dilute acid, and was thus separated and purified from most of the yolk. Dilutions of this material also gave positive intracutaneous reactions in four cases of granuloma inguinale, although quantitatively less marked than those obtained with suspensions of the organisms. Negative reactions were obtained in nine control cases.

Precipitin tests made by utilizing solutions of this capsular material and undiluted inactivated serum from 20 cases of granuloma inguinale were positive in 19 and negative in one. Similar tests with 66 control sera were negative in all but two, including five out of six cases with positive Frei skin reactions and 15 cases with positive serological reactions for syphilis.

Complement fixation reactions were positive in 12 of 15 cases of granuloma inguinale, and negative in 18 of 19 controls (excluding anticomplementary sera in both groups).

To check further the antigenic properties of the organisms, two hens were given repeated inoculations of infected yolk. Both gave positive intracutaneous reactions and positive precipitin reactions to the materials used in testing the human cases.

These tests, as pointed out by the authors, require further study and elaboration to establish their value as diagnostic procedures. They have shown a sufficiently high degree of specificity, however, to constitute strong evidence that the Donovan bodies are actually the causative agent of granuloma inguinale. The crucial test, reproduction of the disease in man by means of the cultures, remains to be carried out. Eventually attempts to do this will doubtless be forthcoming.

## REVIEWS

*The Reticulo-Endothelial System in Sulfonamide Activity* By FRANK THOMAS MAYER, Ph D, Assistant Professor of Pharmacognosy and Pharmacology in the University of Illinois 232 pages, 27.5 × 20.5 cm 1944 The University of Illinois Press, Urbana, Illinois Price, \$2.50 paper bound, \$3.00 cloth bound

This doctor's thesis is a timely brochure on the sulfonamide drugs. The thesis gives an excellent review of the historical development of the sulfonamide drugs with more than 600 references. The various theories of the mechanism of action of the sulfonamides which have been held tenable from time to time are discussed and evaluated. Special reference is made to sulfonamide inhibitors such as para-amino-benzoic acid.

In the experimental portion of the thesis, the writer describes various techniques employed to block the reticulo-endothelial systems of laboratory animals. For this purpose, he found the rabbit the most suitable animal. A colloidal solution of thorium dioxide (Thorodrast) served to provide a plethora of fine particles in the blood stream to blockade the reticulo-endothelial system. A carefully cultured strain of *Staphylococcus aureus* served as the infecting organism. In the rabbits, which had received intravenous injections of "Thorodrast" the administration of sulfathiazole produced urinary excretion of the unacetylated drug. In the normal animal, approximately 25 per cent of the compound was excreted in an acetylated form. It was concluded that the cells of the reticulo-endothelial system accomplish the acetylation.

Rabbits unmedicated died within 24 hours after inoculation with the culture of the organism. These animals could be saved by sulfathiazole medication. In those animals inoculated with *Staphylococcus aureus*, whose reticulo-endothelial systems have been blockaded with "Thorodrast," sulfathiazole failed to save their lives. It was concluded that in any theory of sulfonamide activity, the reticulo-endothelial system of the host must be given a major consideration.

J C K, JR

## BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*The Chemistry and Physiology of Hormones* Publication of the American Association for the Advancement of Science Publication Committee HANS JENSEN, F C KOCH, and ABRAHAM WHITE Edited by FOREST RAY MOULTON 243 pages, 26.5 × 19 cm 1944 American Association for the Advancement of Science, Washington, D C Price, \$3.50 (to members), \$4.00 (to others)

*Proceedings of the Rudolph Vnchow Medical Society in the City of New York* Volume III 1944 Edited by the Publication Committee FRANZ M GROEDEL, M D, BRUNO KISCH, M D, and ERWIN SCHIFF, M D 103 pages, 25.5 × 18 cm 1945 Brooklyn Medical Press, Inc New York, N Y Price, \$2.00

*Clinical Case-Taking* Third Edition By GEORGE HERRMANN, M D, Ph D 192 pages, 20 × 13 cm 1945 C V Mosby Company, St Louis Price, \$1.75

*The Doctor's Job* By CARL BINGER, M D 243 pages, 22 × 15 cm 1945 W W Norton & Company, Inc, New York, N Y Price, \$3.00

*Tropical Medicine* Fifth Edition By SIR LEONARD ROGERS, KCSI, CIE, LL.D., M.D., B.S., FRCP, FRCS, FRS, and SIR JOHN W.D. MEGAW, KCIE, B.A., M.B., Hon. D.Sc. (Queen's University, Belfast) 518 pages, 23.5 × 15.5 cm 1944 The Williams and Wilkins Company, Baltimore Price, \$6.50

*Radiologic Examination of the Small Intestine* By ROSS GOLDEN, M.D. 239 pages, 26 × 18 cm 1944 J.B. Lippincott Company, Philadelphia Price, \$6.00

*Clinical Roentgenology of the Digestive Tract* Second Edition By MAURICE FELDMAN, M.D. 769 pages, 23.5 × 16 cm 1945 The Williams and Wilkins Company, Baltimore Price, \$7.00

*The Specificity of Serological Reactions* Revised Edition By KARL LANDSTEINER, M.D. With a Chapter on Molecular Structure and Intermolecular Forces by Linus Pauling 310 pages, 21.5 × 14.5 cm 1945 Harvard University Press, Cambridge, Massachusetts Price, \$5.00

## COLLEGE NEWS NOTES

### A C P BOARD OF REGENTS AND COMMITTEES WILL MEET JUNE 9-10

The various committees, including the Committee on Credentials, of the American College of Physicians will meet at the Philadelphia Headquarters on June 9, the Board of Regents, on June 10. This meeting was postponed from the one first scheduled at St. Louis, May 3 to 5, owing to regulations of the Office of Defense Transportation. The regulations of the ODT still remain unchanged, hence, there is at present no prospect of an Annual Business Meeting for the election of Officers, Regents and Governors, nor of a meeting of the Board of Governors, because such a meeting would exceed in attendance the maximum of fifty, the limit set by the ODT. Present Officers, Regents and Governors will continue to serve until a regular election can take place.

All candidates whose proposals were executed and filed with the Executive Offices of the College by May 10, thirty days in advance of June 9, will be passed upon by the Committee on Credentials and the Board of Regents. Elections will be announced in these columns and formal notices will be mailed to each successful candidate as promptly as possible.

Oral examinations of the American Board of Internal Medicine for candidates from the eastern territory will be held at Philadelphia, June 6, 7 and 8. (See complete schedule later in the News Notes section of this issue.)

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### ADDITIONAL A C P MEMBERS IN THE ARMED FORCES

Dr. Elizabeth Brakeley, F A C P, Montclair, N. J., has been commissioned a Major in the U. S. Public Health Service and will shortly go abroad in the service of the United Nations Relief and Rehabilitation Administration, to be gone for at least a year. This brings the total number of members who have entered upon military duty to 1,857.

The following members of the College have been honorably discharged:

Charles R. Castlen, Lieutenant Colonel, (MC), A. U. S.—Glendale, Calif.

Roger S. Mitchell, Jr., Major, (MC), A. U. S.—Glens Falls, N. Y.

W. Grady Mitchell, Lieutenant Commander, (MC), U. S. N. R.—San Angelo, Tex.

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Lt. Comdr. J. LaMonte Zundell, (MC), U. S. N., Liberated from Bilibid Prison, Manila.

Lt. Comdr. Zundell was among those rescued on February 4 from the Japanese Military Prison at Bilibid Hospital, Manila. Comdr. Zundell is an Associate of the College and was reported as a "prisoner of war" at the time of the fall of the Philippines. It was not until February 21 that his wife, in Grosse Pointe, Mich., learned of his rescue, as cables sent by Comdr. Zundell never came through. Finally notice came from the Bureau of Medicine and Surgery. She was totally unable to get direct communications to him, but early in March he arrived in San Francisco and proceeded to Grosse Pointe, where he was granted a fourteen day stop-over en route to the U. S. Naval Medical Center at Bethesda, Md., where he has been undergoing treat-



ment Comdr Zundell had suffered from beri-beri and had been reduced in weight to 105 pounds when liberated. His ill health, however, while a prisoner, worked out fortunately for him, because he was left behind as too sick to be included on the ill fated prisoners of war ship, on which the Japanese transferred some 1600 persons from Manila to Japan, the ship being sunk by United States bombs. It is not known how many of the prisoners were rescued from the sinking, but among those aboard were several friends of the Zundells, from whom no word has ever been heard. However, rumor has it that only approximately 300 of the prisoners were lost in the sinking and the rest of them are thought to have been transferred to another ship.

Lt Comdr William M Siliphant, (MC), U S N, also an Associate of the College, was liberated at the same time from the Bilibid Hospital, a report of which was published in the April issue of this journal.

### GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged

#### *Reprints*

Frank N Allan, F A C P, Boston, Mass—1 Reprint  
 J Edward Berk, F A C P, Captain, (MC), A U S—1 Reprint  
 Leon Bromberg, F A C P, Commander, (MC), U S N R—1 Reprint  
 William J Bryan, Jr, F A C P, Tulsa, Okla—1 Reprint  
 N W Chaikin, F A C P, New York, N Y—1 Reprint  
 James M Flynn, F A C P, Rochester, N Y—1 Reprint  
 Hyman I Goldstein (Associate), Camden, N J—1 Reprint  
 Harold J Harris, F A C P, Lieutenant Commander, (MC), U S N R—3 Reprints  
 Thomas A Lebbetter, F A C P, Colonel, R C A M C—Report of the National Health Survey, Canadian Medical Procurement and Assignment Board  
 Samuel Morrison, F A C P, Lieutenant Colonel, (MC), A U S—1 Reprint  
 Franklin B Peck, F A C P, Indianapolis, Ind—1 Reprint  
 Lawrence E Putnam (Associate), Washington, D C—1 Reprint  
 Leonard B Shpiner (Associate), Captain, (MC), A U S—2 Reprints

Gifts other than by members of the College include the following

"Diet and Disease," by Dr C G McDonald, F R A C P, Sydney, Australia  
 "Diet Formulary," Bureau of Medicine and Surgery, Navy Department, by Dr George Schmitt, F A C P, Farragut, Idaho  
 "The Story of Penicillin, Yellow Magic," presented by Dr Charles E Dutchess, Medical Director of the Schenley Laboratories, New York City  
 "Courage and Devotion Beyond the Call of Duty," presented by Dr A L Rose, Vice President, Mead Johnson & Company, Evansville, Ind  
 "Courage and Devotion Beyond the Call of Duty" is a partial record of official citations to medical officers in the United States Armed Forces during World War II. This is a preliminary edition, dated November, 1944. Among those listed are the following members of the American College of Physicians

Colonel Otis O Benson, Jr (Associate), (MC), U S A—Legion of Merit,  
 Captain Isidore Brill, F A C P, (MC), A U S—the Army Air Medal,  
 Captain John H Chambers, F A C P, (MC), U S N, and Capt John M McCants, (MC), U S N—a citation for distinguished service to Mobile Hospital Unit

No 2, at the time of the attack on Pearl Harbor, December 7, 1941, the Commanding and Executive Officers being, respectively, Captain Chambers and Captain McCants, Lieutenant Colonel Garfield G Duncan, F A C P, (MC), A U S—Legion of Merit,

Major Donald D Flickinger (Associate), (MC), U S A—Distinguished Flying Cross,

Brigadier General Leon A Fox, F A C P, (MC), U S A—Distinguished Service Medal,

Colonel Dale G Friend, F A C P, (MC), A U S—Legion of Merit,

Colonel James O Gillespie, F A C P, (MC), U S A—Distinguished Service Medal,

Lieutenant Colonel William R Hallaran, F A C P, (MC), A U S—Legion of Merit,

Commander Bartholomew W Hogan, F A C P, (MC), U S N—Purple Heart,

Brigadier General Edgar Erskine Hume, F A C P, (MC), U S A—Oak Leaf Cluster to the Distinguished Service Medal,

Colonel Walter S Jensen, F A C P, (MC), U S A—Legion of Merit,

Captain Richard A Kern, F A C P, (MC), U S N R—Letter of Commendation,

Commander William Harry Leake, F A C P, (MC), U S N R—Special Citation,

Major General James C Magee, F A C P, (MC) U S A—Distinguished Service Medal,

Lieutenant Edward P McLarney, F A C P, (MC), U S N—Navy Cross,

Captain Alphonse McMahon, F A C P, (MC), U S N R—Special Citation by Admiral Halsey,

Lieutenant Ferrell H Moore, F A C P, (MC), U S N R—Legion of Merit,

Colonel Maurice C Pincoffs, F A C P, (MC), A U S—Legion of Merit,

Commander James J Saperro (Associate), (MC), U S N—Distinguished Service Medal,

Brigadier General James S Simmons, F A C P, (MC), U S A—a special medal in connection with the work of the United States Typhus Commission,

Colonel Frank B Wakemann, F A C P (MC), U S A—Legion of merit posthumously,

Captain Joel J White, F A C P, (MC), U S N—Presidential Unit Citation and Legion of Merit,

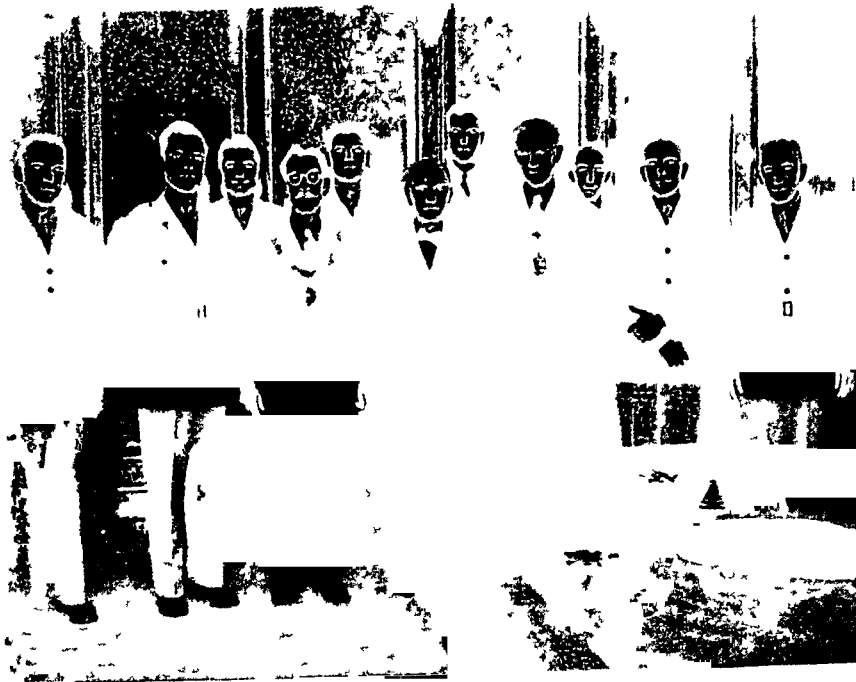
Lieutenant Colonel Charles T Young, F A C P, (MC), U S A—Legion of Merit

In the book now deposited in the College Library appears the specific citation in each of the above cases

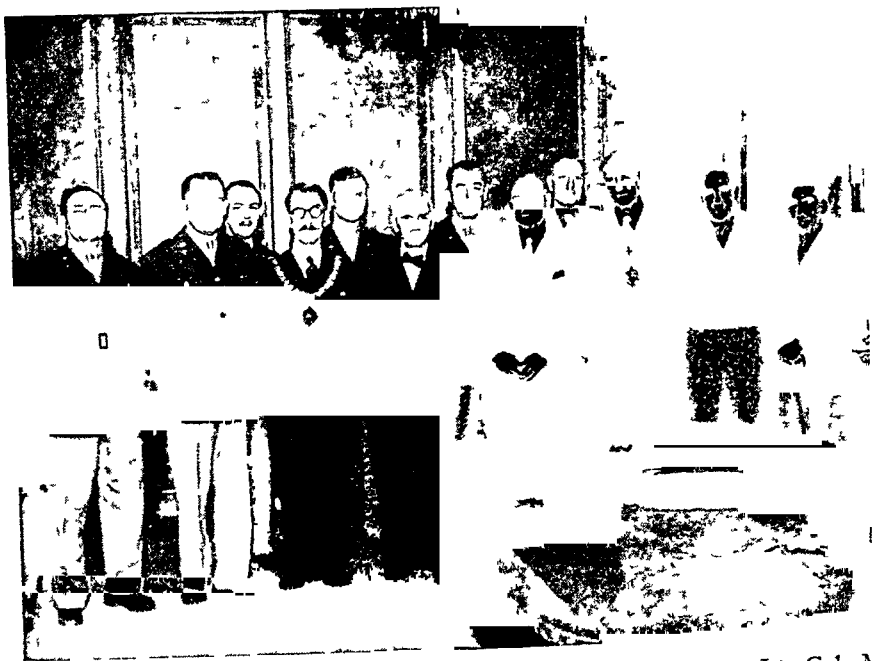
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American doctors from U S Military hospitals in England were among an audience of about 400 physicians and surgeons who attended a lecture on "Penicillin" by its discoverer Sir Alexander Fleming at Nottingham. The doctors were entertained to lunch by the Lord Mayor of Nottingham and the picture shows a group of Americans with the Lord Mayor, Professor Fleming and the Sheriff of Nottingham.

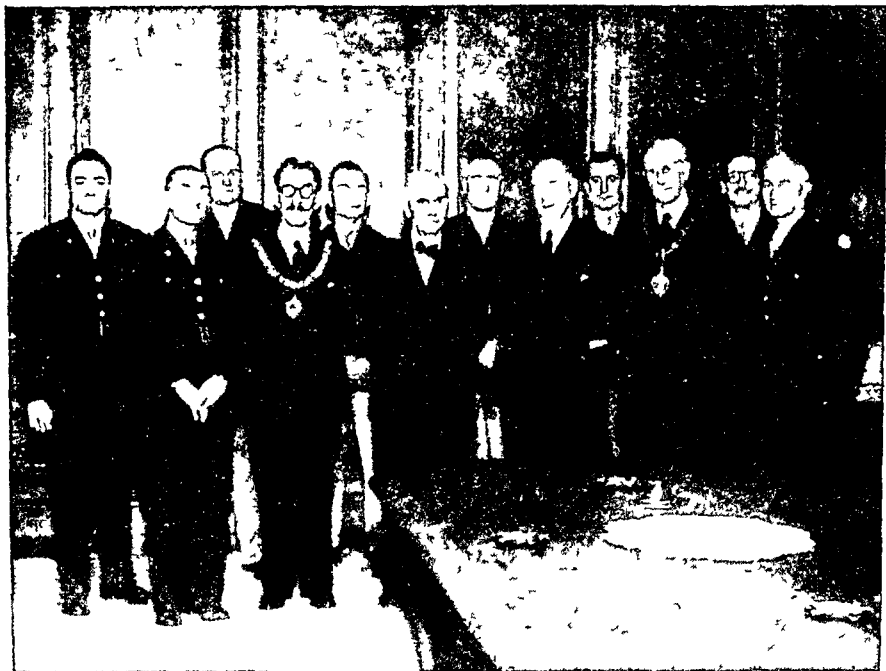
The Professor said America had now beaten the world in the manufacture of Penicillin by cultivating it in tanks containing scores of thousands of gallons



Left to right Major S C Meigher, 1036 Pelhamdale Ave, Pelham Manor, N Y, Lt Col L E McKelvey, 500 Selby Blvd, Worthington, Ohio (Colonial Hills), Capt C C Chumbley, 3101 West End Ave, Nashville, Tenn, The Lord Mayor of Nottingham, Major C F Vorder Bruegge, 1993 Linden Ave, Memphis 4, Tennessee, Prof Sir Alexander Fleming, Major D F H Murphey, 3235 7th Ave, No, St Petersburg, Florida, The Sheriff of Nottingham, Lt Col W A Cooper, 333 E 68th St, New York, N Y, Col C L Kirkpatrick, Glencourt Apartment, Nashville, Tennessee, Lt Col L S Meriwethe, 200 Lamar Life Bldg, Jackson, Mississippi



Left to right Major Abramson, 60 Kilsyth Rd, Brookline, Mass, Lt Col McCann, 1792 Hilcrest St, Minneapolis, Minn, Major Lauer, 638 Arlington Place, Chicago, Illinois, The Lord Mayor of Nottingham, Major McGregor, 1809 4th Ave, N, Great Falls, Mont, Prof Fleming, Major Shute, New Orleans, Louisiana, Dr Scott, Major McDouglas, Booneville, Mississippi, The Sheriff of Nottingham, Capt Mell, 1074 Ashmount Ave, Oakland, Cal, Major Falk, 1734 36th Ave, San Francisco, California



Left to right Major D R Kaufman, 5430 Netherland Ave, Riverdale, New York, Major F M Acree, 1302 Washington Ave, Greenville, Mississippi, Lt Col J D Maloney, 114 Sayles St, Lowell, Mass, The Lord Mayor of Nottingham, Major J J Foley, Hartford, Connecticut, Prof Fleming, Major G E Quigley, 18 Rogers St, Newton 58, Mass, Dr Scott, Major B F Thompson, Columbia, Mississippi, The Sheriff of Nottingham, Major Hyman L Naterman, 41 Hatherly Rd, Brighton, Massachusetts, Major W Sterling Clark, Ventura, California

#### A C P POSTGRADUATE COURSES

The spring Postgraduate Courses offered by the American College of Physicians were, with only a single exception, greatly oversubscribed. According to regulations of the Office of Defense Transportation, no course was allowed to exceed fifty registrants from outside of the city and environs where the Course was given. In one or two instances the total registration of courses exceeded the maximum of fifty, but only owing to the fact that the excess number came from the local city.

The Committee on Postgraduate Courses exceedingly regrets that it is not at present possible, under war conditions, to provide facilities that will fulfill the demand among physicians for these courses—in fact, we have been at present unable to accommodate all of the members of the College who desire these courses and have had to restrict the registration almost wholly to members of the College. The basic registration fee is \$20 per week to members of the College, \$40 per week to non-members of the College, free to medical officers of the Armed Forces.

The following table gives a summary of registration for the various courses

Course	Associates	Fellows	Non Members	Total	Army	Navy	US P H S	Civilians
No 1	19	42	8	69	11	6	2	50
No 2	14	23	0	37	4	0	1	32
No 3	9	20	16	45	8	0	4	33
No 4	14	35	1	50	7	1	0	42
No 5	6	24	0	30	4	0	0	26

Course No 1, CARDIOLOGY, Columbia University College of Physicians and Surgeons, New York, March 19-24, 1945

Course No 2, MECHANICS OF DISEASE, Harvard Medical School and Peter Bent Brigham Hospital, Boston, April 9-21, 1945

Course No 3, CLINICAL MEDICINE WITH SPECIAL EMPHASIS UPON THE HEMATOLOGIC VIEWPOINT, Ohio State University College of Medicine, Columbus, April 16-21, 1945

Course No 4, GASTRO-INTESTINAL DISEASES, Graduate Hospital, University of Pennsylvania, Philadelphia, April 23-28, 1945

Course No 5, APPLICATIONS OF PSYCHIATRY TO THE PRACTICE OF INTERNAL MEDICINE, University of Wisconsin Medical School, Madison, April 30-May 5, 1945

*Autumn, 1945, Courses* Interested readers should watch these columns in succeeding numbers for announcements concerning the Autumn Schedule of Courses. Members are encouraged to send in suggestions to the Executive Offices of the College.

The Committee on Postgraduate Courses and the Board of Regents will arrange several courses during October, November and December. At this time definite arrangements have been made for the repetition of the course in CARDIOLOGY under the Directorship of Dr. Paul D. White at the Massachusetts General Hospital, Boston, during the week of November 5, 1945.

#### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

Colonel William C. Menninger, F A C P, Chief Consultant in Psychiatry to the Surgeon General, was the featured speaker at the Mental Health in Wartime forum, the first of a series to be held by the Washington (D C) Metropolitan Health Council. He stressed the fact that the neuropsychiatric service in the Army provides not only treatment opportunities but preventive measures. He expressed the hope that popular understanding of psychiatry would "definitely dispel the clouds of mystery and the irrational stigmatization of those afflicted with emotional illness and bring about a public demand for the application of psychiatric principles to our legal, our educational, our political and our medical practices."

During March a glider service was inaugurated in the European Theater to evacuate our wounded from Remagen. Observers reported that the shock incident to being "snatched" into the air was absorbed by an improved towing device. It is now possible that gliders may almost eliminate ambulances for hauling our battle casualties long distances over shell torn roads, giving them a faster, smoother ride to the hospital. The gliders serve a dual purpose. Coming into the battle area they can carry twelve litter patients or nineteen walking wounded. Ambulance gliders were first used experimentally by the British in Burma and New Guinea.

#### Advancements in Rank

##### From Major to Lieutenant Colonel

Thomas Hale Ham, F A C P, Brookline, Mass

Joe Hollis Little, F A C P, Mobile, Ala

Winthrop Wetherbee, Jr, F A C P, Boston, Mass

##### From Captain to Major

Marvin R. Corlette, F A C P, Pasadena, Calif

## NATIONAL FOUNDATION FOR INFANTILE PARALYSIS SCHOLARSHIPS

Scholarships for training in physical therapy under the \$1,267,600 program of the National Foundation for Infantile Paralysis are available immediately for classes commencing in June and July, according to Basil O'Connor, President of the Foundation. These scholarships are for nine to twelve months courses in private schools of physical therapy. The scholarships will cover tuition and maintenance in accordance with the student's needs.

The training program will be carried out with the assistance of a special committee under the chairmanship of Dr. Irvin Abell, Louisville, Ky. Candidates must have two years of College, including biology and other basic sciences, or be graduates of accredited schools of nursing or physical education. Applications should be made to the National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y., or to the American Physiotherapy Association, 1790 Broadway, New York 19, N. Y.

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Under the personal direction of Dr. Louis N. Katz, F. A. C. P., Director of Cardiovascular Research, the annual intensive two weeks course in electrocardiography for graduate physicians will be given at Michael Reese Hospital, Chicago, August 20 to September 1, 1945. Group and individual instruction will be given, the course is open to beginning and advanced students in electrocardiography.

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Lieutenant Commander Howard G. Bruenn, (MC), U. S. N. R., F. A. C. P., was the Navy physician assigned to look after the late President, Franklin Delano Roosevelt, during his stay at Warm Springs, where he died on April 12. According to radio announcements, Dr. James E. Paullin, F. A. C. P., former President of the American College of Physicians, Atlanta, was immediately called in consultation at the time of the President's collapse.

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Dr. Elmer L. Sevringhaus, F. A. C. P., Professor of Medicine at the University of Wisconsin Medical School and College Governor for the State of Wisconsin, is absent from this country for several months on a special mission to Italy.

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## RETIRING MEDICAL OFFICER, U. S. ARMY, SEeks APPOINTMENT

A Fellow of the American College of Physicians, born in 1882, has been retired for age as Colonel in the Medical Corps of the Regular Army. He is immediately available for an appointment, preferably in the East. He has had wide experience in public speaking and in liaison work with the public and with the general medical profession. He is well prepared to teach preventive medicine or tropical medicine, but is also interested in administrative work in connection with a medical school, medical society, or departments of health. He attended Wesleyan University for three years and graduated in medicine from Columbia University College of Physicians and Surgeons in 1908. He graduated from the Army Medical School in Washington in 1912 and has had the usual Army career, with assignments at Army installations all over the United States, Panama, Hawaii, the Philippines and elsewhere. He has published several worthy papers, is in exceptionally good health and of keen mental capacities.

The College by acting as an intermediary will be performing a valuable service to this Fellow, as well as to any institution through which an appointment may develop. Address the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

Dr William Harvey Perkins, F A C P, Dean of Jefferson Medical College of Philadelphia, will receive the honorary degree of Doctor of Science at the June commencement exercises of Dickinson College

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Colonel Maurice C Pincoffs, (MC), A U S, F A C P, who has served almost from the beginning of the war as Consultant in Medicine for the Pacific Theater, has been made Public Health Administrator for the City of Manila His address is Advanced Detachment Headquarters, U S A F F E, A P O 501, c/o Postmaster, San Francisco, Calif

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Brigadier General Hugh J Morgan, F A C P, Consultant to the Surgeon General of the U S Army, has been touring the European War Theater According to the lay press of April 7, General Morgan had an audience with Pope Pius in Vatican City

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Dr Russell S Boles, F A C P, was recently reelected President of the Medical Board of the Philadelphia General Hospital, this being his third consecutive year

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The Sugar Research Foundation announced on April 16, 1945, six grants to scientists for research into new industrial and nutritional uses for sugar The awards amount to \$45,400, bringing to more than \$300,000 the total funds which the Foundation has made available to science One of the grants, \$2500 for one year, to study further the body's relative rate of absorption of sucrose, dextrose and levulose, was made to Dr I M Rabinowitch, F A C P, of McGill University Faculty of Medicine, Montreal

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Dr Christopher G Parnall, Sr, F A C P, for the past twenty-one years Medical Director of Rochester General Hospital, has resigned, effective October 1 Dr Parnall will devote his time to consultation in hospital planning and construction, a work in which he has been engaged for the past thirty years He has been retained as consultant on several large projects costing several millions of dollars His most recent assignment was that of director of the technical staff for the Dewey Commission which investigated the care of the mentally ill in the State of New York

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Dr H Vernon Madsen (Associate) has completed his work at the Henry Ford Hospital, Detroit, and has opened an office for practice at 525 Sycamore Street, Waterloo, Iowa He will give special attention to diseases of the chest

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Dr Franklin C Cassidy, F A C P, formerly stationed at the Veterans Administration, Walla Walla, Washington, as Clinical Director, has been promoted and transferred to the Veterans Administration, Waukesha, Wisconsin, as Manager

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Dr Eugene P Pendergrass, F A C P, is Chairman of the Board of Chancellors of the American College of Radiology Under his leadership the College has carried on an alert and an aggressive program that has accomplished and is accomplishing some definitely desirable results Dr Pendergrass' statement, published in a recent bulletin of the College, would be worthy of any organization, "our fullest devotion in time, effort and serious study will be demanded in the critical years ahead if we are to fulfill the obligations we have assumed for the protection of our specialty and the improvement of service in the care of the sick "

A considerable number of physicians are Fellows of both the American College of Radiology and the American College of Physicians, hence this brief report will be of specific interest to many and of general interest to all. The American College of Radiology has the following problems of particular importance under consideration at present: Radiology in prepayment plans, extension of facilities for training residents in radiology, the maintenance of proper standards in the relations between radiologists and hospitals, malpractice insurance, inspection of hospital x-ray departments, the distribution of radiological service.

It is interesting to note that the Annual dues of Fellows of the American College of Radiology are at present \$25 per annum, with a prospect of materially increasing the amount in the future. Fellowship dues in the American College of Physicians are \$15 per annum, with certain reductions therefrom for full-time teachers, laboratory and research workers, with full waiver of dues during the war to medical officers on active military duty.

The American College of Radiology will cooperate with other existing groups in national post-war planning for medical service, but it will, furthermore, have its own individual program for taking care of its own members, following discharge from military service. Its Commission on Education is undertaking a study of this matter and plans are under way for the preparation of a "Manual of Graduate Training" for the use of hospitals and radiologists who have not heretofore trained residents. Plans will also be completed for a series of short postgraduate Courses to be conducted in various sections of the country during the next few years.

#### ORAL EXAMINATIONS, AMERICAN BOARD OF INTERNAL MEDICINE

Oral examinations will be held during 1945 in accordance with the following schedule. Candidates who have been advised of the successful completion of the written examination will be accepted:

(1) Philadelphia, Pa., June 6-7-8. For candidates from Connecticut, Delaware, District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, South Carolina, Vermont, Virginia, West Virginia. (Closing date, May 5)

(2) New Orleans, La., May 21-22-23. For candidates from Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Oklahoma, Tennessee, Texas. (Closing date, May 5)

(3) Chicago, Ill., June 27-28-29. For candidates from Illinois, Indiana, Iowa, Kansas, Kentucky, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin. (Closing date, May 12)

(4) San Francisco, Calif., Oct. 15-16-17. For candidates from Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming. (Closing date, Sept. 1)

Candidates who have been notified of the approval of their applications for admission to an oral examination in a subspecialty will be admitted at the time and place of the oral examination in internal medicine, provided the oral examination in internal medicine is satisfactory.

Candidates with an A P O or Fleet P O address who find it possible to report, please advise the central office of the Board as to the most convenient place on the schedule. The Board will make every effort to meet their convenience.

The Board will appreciate your consideration if you will not request admission unless you are reasonably sure of being present. The schedule must of necessity be fixed within geographical limits, but will be sufficiently flexible to accommodate candidates in the armed forces if they have a change of station after the closing date for the acceptance of applications.



Candidates previously certified in Internal Medicine will be admitted to oral examination in their subspecialty in accordance with the above schedule if application has been approved and notification has been received

Write immediately for application form to the American Board of Internal Medicine, 1301 University Ave., Madison 5, Wis (Editor's Note The above notice received for publication on April 16, 1945, too late for inclusion in the April issue of this journal)

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Dr Samuel M Poindexter, F A C P, Boise, College Governor for Idaho, was recently reappointed a member of the State Board of Medical Examiners

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Dr Theodore R Van Dellen, F A C P, has been appointed health editor of the Chicago *Tribune*

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Dr William J Mallory, F A C P, Washington, is one of a committee of three who have recently completed the writing of the history of the Medical Society of the District of Columbia

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Dr William M LeFevie, F A C P, was recently appointed a member of the Muskegon (Mich) Board of Health

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Dr Raymond Hussey, F A C P, Detroit, is dean of the School of Occupational Health and professor of preventive medicine at Wayne University College of Medicine

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Col James E Ash, F A C P, Director of the Army Institute of Pathology, Washington, delivered the tenth Harrison S Martland Lecture at the Newark (N J) Academy of Medicine, March 28, on "The Army Institute of Pathology and Its Contribution to the Study of Diseases Prevalent in the Military Air Group"

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The William Freeman Snow Medal for distinguished service to humanity was awarded to Major General Merritte W Ireland, F A C P, at the 32nd annual meeting of the American Social Hygiene Association at Chicago recently General Ireland was a former Surgeon General of the U S Army

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Recently Col John B Youmans, F A C P, Director of the Nutrition Division of the Medical Corps of the U S Army, addressed the University of Virginia chapter of Alpha Omega Alpha on "Principles Underlying the Early Diagnosis of Nutritional Deficiency Disease"

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A Symposium on Industrial Medicine was conducted at the New York Post-Graduate Medical School, April 2-6, under the direction of Dr Harry J Johnson, F A C P, and Dr Frank R Ferlamo. Among those on the faculty were Dr C Charles Burlingame, F A C P, Dr Maurice Bruger, F A C P, Dr Charles A Poindexter, F A C P, Dr A Wilbur Duryee, F A C P, Dr Dwight O'Hara, F A C P, and Dr John D Currence, F A C P

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Dr Hubert M English, F A C P, has been elected president of the Gary (Ind) Board of Health

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Dr J C Geiger, F A C P, San Francisco, was recently notified by the Consul General of Portugal, Euclides Goulart da Costa, that the Portuguese Government

and its Premier Salazar have conceded to him the most ancient and revered European and Catholic order, the Cavaleiro da Ordem de Cristo (Order of Christ), with the following citation "For great personal and professional merit in public health, and for important services to the Portuguese people of Portugal and of California"

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Dr Frank H Krusen, F A C P, head of the section on physical medicine, Mayo Clinic, Rochester, and Dr George Morris Piersol, F A C P, director of the division of physical medicine, University of Pennsylvania, Philadelphia, gave two of the three lectures of a course in physical medicine sponsored by the District of Columbia Medical Society during April, their subjects being, respectively, "The Future of Physical Medicine" and "Clinical Aspects of Physical Medicine"

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The Charles V Chapin Memorial Award of the Rhode Island Medical Society was made to Dr Reginald Fitz, F A C P, Boston, on February 5. Dr Fitz delivered the Chapin Oration during the meeting of the Rhode Island Medical Society in May 1944, but the medal was not ready at that time and was formally presented on the date first referred to

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Dr Tom D Spies, F A C P, assistant professor of medicine, University of Cincinnati College of Medicine, gave the first Edward H Cary Lecture at the Southwestern Medical College of the Southwestern Medical Foundation, Dallas. This lectureship was established as an expression of appreciation to Dr Edward H Cary, president of the Foundation, for his work in connection with the Foundation and the Medical School

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Dr Warfield T Longcope, F A C P, Baltimore, is a vice president of the American Association for the Advancement of Science, representing the field of medical science. Dr Anton J Carlson, F A C P, Chicago, has recently retired as president

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The Long Island College of Medicine, Brooklyn, and the Medical Society of the County of Kings, through a joint committee on postgraduate education, are offering numerous postgraduate courses for local physicians. Most of the courses began during April and will be continued for terms varying from 8 to 16 sessions, 1 or 2 meetings per week.

Among courses listed are the following: ALLERGY, Dr George A Merrill, F A C P, Director, ARTHRITIS, Dr A S Gordon, F A C P, Director, ELECTROCARDIOGRAPHY, Dr S R Slater, F A C P, Director, ELECTROCARDIOGRAPHY AND CLINICAL CARDIOLOGY, Dr Charles Shookhoff, F A C P, Director, GASTROENTEROLOGY, Dr Benjamin M Bernstein, F A C P, Director, CLINICAL HEMATOLOGY, Dr Maurice Morrison, F A C P, Director, HYPERTENSION AND NEPHRITIS, Dr Harry Mandelbaum, F A C P, Director, CLINICAL PEDIATRICS, Dr Abraham M Litvak, F A C P, Director, ENDOCRINE DISEASES AND DISORDERS IN CHILDREN AND ADOLESCENTS, Dr Maurry B Gordon, F A C P, Director, PATHOLOGY OF INTERNAL MEDICINE, Dr Jacob M Ravid, F A C P, Director

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Dr A C Ivy, F A C P, Chicago, has been appointed for a three year term to membership on the National Advisory Cancer Council of the U S Public Health Service

Dr George E Wakerlin, F A C P, Chicago, has been elected chairman of the Chicago Cancer Committee

Dr Wakerlin has been appointed assistant dean in charge of teaching and research at the Rush-Presbyterian Hospital, a division of the University of Illinois College of Medicine

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Captain Vincent Hernandez (Associate), (MC), U S N, was recently awarded the Bronze Star, "for meritorious achievement as force medical officer on the staff of Commander Air Force, United States Atlantic Fleet, from June 1943 until January 1945. Skilfully coordinating the work of medical officers of the Air Force, Atlantic Fleet, with that of naval air stations basing fleet aviation units, Captain Hernandez organized and supervised the activities of the officers under his jurisdiction and, by his untiring efforts and painstaking attention to particular needs, effected measures to insure the physical fitness, endurance and resistance of flying and maintenance personnel engaged in the widespread battle of the Atlantic. His exceptional success in this vital service reflects the highest credit on Captain Hernandez and the United States Naval Service"

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The late Dr Logan Clendening, F A C P, left a bequest of \$50,000 to the University of Kansas Endowment Association to be used for the Department of Medical History

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The New York Academy of Medicine will conduct its Eighteenth Graduate Fortnight October 8-19. The general theme will be "Contributions of the War Effort to Medicine"

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Dr Roger S Mitchell, Jr, F A C P, of Glens Falls, New York, retired from active duty as Major, (MC), A U S, on May 4, 1945, and plans to work at the North Carolina Sanatorium, Sanatorium, N C, starting June 1, continuing until he has regained his health

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The American College of Chest Physicians, with a membership in 23 countries, has cancelled its annual meeting scheduled to be held at Philadelphia, June, 1945

The Executive Council of the College voted to hold a business meeting of the Board of Regents at Chicago, June 17

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As the result of a nationwide poll among leaders in medical science, Dr Edwin J Cohn, Professor of Biochemistry at Harvard University, has been chosen as the first winner of The Passano Foundation award. Presentation of the \$5,000 cash award will be made at an appropriate ceremony in historic Osler Hall of the Medical and Chirurgical Faculty of Maryland, in Baltimore, on the night of May 16

The Foundation, which was established in 1944 by The Williams and Wilkins Company, Medical Publishers, of Baltimore, proposes to aid in any way possible the advancement of medical research, especially research that bears promise of clinical application. For the encouragement of such research the Foundation has established the award as one of its activities

Dr Emil Novak, Associate in Gynecology in the Johns Hopkins University Medical School, Dr Nicholson J Eastman, Professor of Obstetrics in the Johns Hopkins University Medical School, Dr George W Corner, Director of the Embryological Laboratory of the Carnegie Institution of Washington, represent the medical profession on the Board of Directors of The Foundation

Dr Cohn is distinguished for his work on the fractionation of blood. Beginning in 1919 with a study of blood and blood proteins, Dr Cohn's research has progressed until it has yielded a spectacular group of five principal fractions of blood plasma which hold untold promise of usefulness in medical science

Fraction I contains fibrinogen, a substance which forms blood clots when activated by thrombin and from which a series of fibrinogen plastics can be made and fashioned into any shape and to any consistency from elastic to solid. Because this plastic material can be absorbed in the body it has many potential uses in surgery.

Fraction II contains immune globulin, which is useful in establishing an immunity in such virus diseases as measles.

Fractions III and IV are proteins whose functions and usefulness have not yet been fully exploited, while fraction V contains the plasma albumin proteins which give the plasma its property of combating shock.

Following the presentation of the award by Mr. Edward B. Passano, Chairman of the Board of The Williams and Wilkins Company, Dr. Cohn will read a paper concerning the applications of his work on blood plasma to the field of clinical medicine.

#### THE WAR-TIME GRADUATE MEDICAL MEETINGS

This joint effort by the American College of Surgeons, the American Medical Association and the American College of Physicians has been quietly and efficiently going forward almost from the first of the War—a program of graduate lectures, demonstrations, ward teaching carried to physicians in Army and Navy installations in all parts of this country. Hundreds of authorities, teachers and practitioners, in the many subdivisions of medicine have been and still are giving their time unstintingly to this worthy work. Enough credit and acknowledgment have not been given either to the faculties or to the many Zone chairmen and committeemen. Let us not forget the fine work the War-Time Graduate Medical Committee (Dr. F. F. Borzell, Chairman, Dr. Alford Blalock and Dr. George Morris Piersol) and its Zone Committees and faculties are doing.

As but one example of the activity of a Zone Committee, District No. 14, embracing Illinois, Indiana and Wisconsin, of which Dr. W. O. Thompson, F.A.C.P., Chicago, is the Chairman, during April alone conducted thirty-four separate sessions with repeated programs, in some instances, at the Billings General Hospital, Wakeman General Hospital, Gardiner General Hospital, Fort Sheridan, Vaughan General Hospital, Great Lakes Naval Hospital, Mayo General Hospital, Camp Ellis, Chanute Field, Camp McCoy, Truax Field, Fort Knox and Nichols General Hospital.

Following appear some of the programs scheduled for the immediate future.

REGION No. 3 (New York)—Dr. O. R. Jones, Chairman, Dr. N. Jolliffe, Dr. H. W. Cave

*Induction Center, Grand Central Palace, New York, New York*

May 18 Deleterious Effects of Drugs on the Hemopoietic System—Dr. Nathan Rosenthal

May 25 Deficiency States and Their Recognition—Dr. H. D. Kluse

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman, Dr. J. S. Rodman, Dr. S. P. Reimann

*U. S. Naval Hospital, Philadelphia, Pennsylvania*

May 18 Health Department Military Liaison in Venereal Disease—Dr. Norman Ingraham

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman, Dr. C. R. Edwards, Dr. C. B. Conklin

*Newton D Baker General Hospital, Martinsburg, West Virginia*

- May 21 Narcosynthesis and Hypnosis—Dr Addison McGuire Duval  
Peripheral Vascular Diseases Due to War-Time Conditions—Dr J Ross Veal
- June 4 Chest Injuries in War—Dr I A Bigger  
Shock—Dr E I Evans
- June 18 Liver Diseases Seen in the Present War—Colonel Balduin Lucke

*A A F Regional Hospital, Langley Field, Virginia*

- May 25 Aviation Medicine—Dr L G Lederer  
Fundamentals of Plastic Surgery—Dr Robert E Moran
- June 29 Gastro-enterology—Dr Lay Martin  
Traumatic Surgery of the Abdomen—Lieutenant R C Wood

REGION No 14 (Indiana, Illinois, Wisconsin)—Dr W O Thompson, Chairman,  
Dr N C Gilbert, Dr W H Cole, Dr W D Gatch, Dr R M Moore, Dr H M Baker,  
Dr E R Schmidt, Dr E L Sevringhaus, Dr F D Murphy

*Gardner General Hospital, Chicago, Illinois*

- May 16 Mental Hygiene and the Prevention of Neuroses in War
- May 23 Wound Healing and Tendon Surgery
- June 6 Peptic Ulcer, Gall Bladder and Liver Diseases
- June 13 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases
- June 20 Chest Diseases and Diseases of the Larynx
- June 27 Low Back Pain

*Station Hospital, Fort Sheridan, Illinois*

- May 16 Peptic Ulcer, Gall Bladder and Liver Diseases
- May 23 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases
- June 6 Chest Diseases and Diseases of the Larynx
- June 13 Low Back Pain
- June 20 Heart Disease and Allied Conditions
- June 27 Bone and Joint Infections

*Mayo General Hospital, Galesburg, Illinois*

- May 16 Chest Diseases and Diseases of the Larynx
- May 23 Low Back Pain
- June 6 Heart Disease and Allied Conditions
- June 13 Bone and Joint Infections
- June 20 Arterial Vascular Disease—Traumatic Lesions
- June 27 Repair of Bone in Fractures and Diseases

*Vaughan General Hospital, Hines, Illinois*

- May 16 Heart Disease and Allied Conditions
- May 23 Bone and Joint Infections
- June 6 Arterial Vascular Disease—Traumatic Lesions
- June 13 Repair of Bone in Fractures and Diseases
- June 20 Diseases of the Kidneys—Urogenital Tract
- June 27 Blood Dyscrasias, Malaria, Filariasis

*Station Hospital, Camp Ellis, Illinois*

- May 16 Arterial Vascular Disease—Traumatic Lesions
- May 23 Repair of Bone in Fractures and Diseases
- June 6 Diseases of the Kidneys—Urogenital Tract
- June 13 Blood Dyscrasias, Malaria, Filariasis
- June 20 High Blood Pressure
- June 27 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment

*Station Hospital, Camp McCoy, Wisconsin*

- May 16 Diseases of the Kidneys—Urogenital Tract
- May 23 Blood Dyscrasias—Malaria—Filariasis
- June 6 High Blood Pressure
- June 13 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment
- June 20 Conditions Affecting Glucose Metabolism
- June 27 Brain and Spinal Cord Injuries

*Station Hospital, Truax Field, Wisconsin*

- May 16 Conditions Affecting Glucose Metabolism
- May 23 Brain and Spinal Cord Injuries
- June 6 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care
- June 13 Plexus and Peripheral Nerve Injuries
- June 20 Dermatological Diseases
- June 27 Burns and Plastic Surgery

*Station Hospital, Chanute Field, Illinois*

- May 16 Dermatological Diseases
- May 23 Burns and Plastic Surgery
- June 6 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment
- June 13 Endocrinology
- June 20 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
- June 27 Psychosomatic Medicine

*Billings General Hospital, Indiana*

- May 16 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment
- May 23 Endocrinology
- June 6 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
- June 13 Psychosomatic Medicine
- June 20 Wound Healing and Tendon Surgery
- June 27 Mental Hygiene and the Prevention of Neuroses in War

*Wakeman General Hospital, Indiana*

- May 16 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
- May 23 Psychosomatic Medicine
- June 6 Wound Healing and Tendon Surgery

- June 13 Mental Hygiene and the Prevention of Neuroses in War  
 June 20 Thrombosis, Thromboplebitis and Anticoagulants in Less Common Peripheral Vascular Diseases  
 June 27 Peptic Ulcer, Gall Bladder and Liver Diseases

REGION No 16 (Missouri, Kansas, Arkansas, Oklahoma)—Dr F D Dickson, Chairman, Dr O P J Falk, Dr H H Turner

*A A F Regional Hospital, Smoky Hill Army Air Field, Salina, Kansas*

- June 14 Gastrointestinal (X-Ray Findings in Abdominal Pathology)—Dr Ira H Lockwood  
 Shock, Burns and Blood Derivatives—Dr Vincent T Williams

REGION No 23 (Nevada, Northern California)—Dr S R Mettier, Chairman, Dr E H Falconer, Dr D N Richards

*Hammond General Hospital, Modesto, California*

- May 30 Laboratory Aids in the Diagnosis of Disease—Dr Jesse Carr  
 June 13 Subacute Bacterial Endocarditis—Dr William J Kerr

*Station Hospital, Hamilton Field, California*

- May 16 Fractures of the Extremities—Dr Carl Anderson  
 May 30 Diagnosis and Treatment of Arthritis—Dr Stacy R Mettier

*Station Hospital, Camp Roberts, California*

- May 19 Diagnosis and Treatment of Arthritis—Dr Hans Waime  
 May 26 The Treatment of Poliomyelitis—Dr Henry D Brainerd  
 June 16 Severe Infections of the Hand—Dr Edmond D Butler

*Station Hospital, Stockton Army Air Base, California*

- May 16 The Treatment of Syphilis—Dr Norman N Epstein  
 May 30 Use and Misuse of Endocrine Preparations—Dr Ernest W Page  
 June 13 Early Ambulation of Surgical Patients—Dr H Glenn Bell  
 June 20 Diagnosis and Treatment of Arthritis—Dr Hans Waime  
 June 27 Injuries to the Knee Joint—Dr Carl E Anderson

*Oakland Area Station Hospital, Oakland, California*

- May 23 Diagnosis and Treatment of Hemorrhagic States—Dr Paul M Aggeler

## OBITUARIES

## DR WILLIAM M DONALD

Dr William M Donald, Fellow of the American College of Physicians since 1917, was born in Allonburg, Ontario, Canada, in the year 1860. After completing one year at the University of Toronto, he entered McGill University Faculty of Medicine which he attended for two years, transferring to Wayne University College of Medicine, where he received his medical degree in 1887.

For many years Dr Donald was Professor of Internal Medicine at Wayne University College of Medicine. At one time he was Chief of Staff and Attending Physician at St Mary's Hospital. In later years he was Consultant in Internal Medicine at the Evangelical Deaconess Hospital and Jefferson Clinic. He was President of the Wayne County Medical Society from 1922 to 1923, President of the Tri-State Medical Association in 1928, former President of the Michigan Health Exposition, Emeritus Member of the Michigan State Medical Society, having served at one time as Chairman of its Medical Section. He served as Chairman of the Wayne County Board of Review during World War I. He received an Honorary Degree of Doctor of Science in Medicine from Wayne University in 1935.

Keenly interested in the science of art, literature and philosophy, Dr Donald established the "Doctors Corner" of the Detroit Public Library, where he gathered many volumes written by physicians on non-medical subjects and fiction.

His inspiring personality, enthusiasm and leadership were demonstrated in his untiring efforts given to the Protestant Children's Home of Detroit for more than thirty years.

His traits of honesty, kindness, charity and determination which shone throughout his life were dimmed only by his death in Grace Hospital, Detroit, December 20, 1944. The Michigan Fellows and Associates of the American College of Physicians join his family and many friends in mourning the passing of this eminent physician.

Dr Donald leaves his son, Lt Colonel Douglas Donald, who served as Governor for the American College of Physicians in Michigan until he was commissioned in the United States Army in 1942, and is now chief of medicine of the 40th Station Hospital in Corsica. A daughter, Mrs Hendrick Pieter Van Gelder of Toronto, Canada, also survives.

P L LEDWIDGE, M D,  
Acting Governor for the State of Michigan

## DR WILLIAM NORTHRUP

Dr William Northrup, Fellow of the American College of Physicians since 1919, was born in Elgin County, Ontario, in 1866. He attended



Trinity Medical College, Toronto, and later received his medical degree from the University of Western Ontario Medical School in London in 1894. He continued his education with postgraduate study at Rush Medical College, Chicago, in Edinburgh, Scotland, London, England, and Breslau, Germany. He later did postgraduate work at the Trudeau School for Advanced Study of Tuberculosis, Saranac Lake, New York.

Dr. Northrup was former President of the Kent County Medical Society, Physician to Michigan State Reformatory, Ionia. He was on the Consulting Staff of Butterworth, St. Mary's and Blodgett Memorial Hospitals, and he was a member of the American Medical Association.

After a long and fruitful life, Dr. Northrup died in Grand Rapids, Michigan, December 9, 1944, at the age of seventy-seven.

P. L. LEDWIDGE, M.D., F.A.C.P.,  
Acting Governor for the State of Michigan

### DR. JOHN WILLIAM FLINN

Dr. John William Flinn, F.A.C.P., Prescott, Arizona, died November 21, 1944, aged 74, of carcinoma of the rectum.

Dr. Flinn was born at Wallace, Nova Scotia, July 10, 1870. On his father's side he was descended from Manxmen, his grandfather having come to Canada from the Isle of Man. His mother's people came to Canada from Scotland. He attended Pictou Academy, and received his medical education at McGill University, Montreal, graduating in 1895. Thereupon he returned to his home town and engaged in general practice until 1898, when he was forced to change climate because of chronic pulmonary tuberculosis from which he had suffered for some time. He came to Arizona, locating in Kingman in September, 1898, where he continued in general practice until 1902, in which year he removed to Prescott. Shortly after his arrival in Prescott he became ill with tuberculous pneumonia which confined him to bed for six months or more. Following recovery Dr. Flinn in 1903 established the Pamsetgaaf Sanatorium. Having been impressed by Osler's dictum regarding tuberculosis, namely, that one should have "pure air, maximum sunshine, equable temperature," he took the first letters of these words and added "good accommodation and food," creating the name "Pamsetgaaf." This sanatorium was the pioneer institution of its sort west of the Mississippi, and here Dr. Flinn carried on his clinical and research work in tuberculosis during the next forty years, continuing as its medical director to the time of his death.

During these four decades of fruitful research and treatment of tuberculosis, Dr. Flinn saw many changes in the concepts regarding the disease, several of which he was instrumental in bringing about. While not a prolific writer, he was a constant reader and keen observer of the work of others, a severe critic of his own practice, the results of which he kept a detailed record, and from time to time he presented carefully prepared papers,

always eagerly received and listened to with respect by his confreres at home and abroad

Because of his own pulmonary condition, Dr Flinn was forced to spend each afternoon at bed-rest, and he became a great student of the literature on tuberculous and other lung diseases. Throughout his whole medical life, in spite of physical handicaps, Dr Flinn gave generously of his time and strength to organized medicine. One of the "famous fighting four" of Yavapai County, he was always in the forefront of any constructive activity of his own county medical society or his state organization. He was made secretary of the Arizona State Medical Association in 1908 and served through 1911, when he was forced to relinquish this office because of physical limitations. He was unanimously elected president of the Association in 1914.

Dr Flinn had three sons and two daughters. Dr Zebud M. Flinn, an Associate of the American College of Physicians, was killed in the Panama Canal Zone in 1940. Dr Robert S. Flinn, like his father, is a Fellow of the College, and the third son, John S. Flinn, is serving as a Captain in the Army of the United States.

Dr John Flinn—a brave warrior, a good friend, a useful citizen, a worthy and respected confrere—we who remain glory in your achievement and will ever cherish your memory.

Selected from an Obituary prepared by  
DR W. WARNER WATKINS, F A C P, Phoenix

### DR HARLAN PAGE MILLS

With the passing of Dr Harlan Page Mills, F A C P, Phoenix, on February 27, 1945, at the age of 72, the pioneer pathologist in Arizona laid down his work and went to his reward.

Dr Mills was born in Worth County, Missouri, August 29, 1873. He attended Maryville (Mo.) Seminary and Missouri Wesleyan College, thereafter receiving his medical degree from the Marion Sims Beaumont College of Medicine in 1902. He served his internship at the Ensworth Hospital, St. Joseph, Mo. He entered general practice at Sheridan, Mo., where he remained for several years. In 1909 he accepted the position of assistant physician at the Missouri State Hospital No. 2, St. Joseph, and was later advanced to pathologist, in which position he served until moving to Phoenix. During this time, in conjunction with another member of the staff, he published the report of a remarkable case which gained wide publicity as "a human hardware store" (J A M A, Jan 21, 1911). This patient, a woman, was found at necropsy to have 1446 different articles of hardware in her stomach, including teaspoons, dozens of nails, tacks, pins, and so forth.

In 1914 Dr Mills became pathologist and assistant psychiatrist at the Arizona State Hospital. In 1917 he became associated with the Pathological Laboratory, then a young and struggling venture. His work in

and with that organization and its affiliation with the two general hospitals in Phoenix, along with St Luke's Home, made up the circle of activities in which Dr Mills spent the remainder of his professional life. Shortly after becoming associated with the Pathological Laboratory, Dr Mills started clinical laboratory work at St Joseph's Hospital in Phoenix, at first bringing all specimens to his office, and later doing the examinations in the hospital with his own microscope which he carried back and forth. From this humble start, the laboratory department of this hospital expanded until it reached such proportions that a full-time pathologist was required. The same development took place at the Good Samaritan Hospital—then known as the Arizona Deaconess Hospital—where clinical laboratory work was started on a shoestring and developed through the years until it too required the services of a full-time clinical pathologist. Dr Mills was made consulting pathologist for each institution upon his retirement from the active direction of their pathologic departments. He was also made an honorary member of the staff of each hospital, in recognition of his more than twenty-five years of service as head of their respective departments.

Dr Mills held membership in the Maricopa County Medical Society (President, 1920), the Arizona Medical Association, Southwestern Medical Association, Radiological Society of North America (formerly a counselor), and he was a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1931. He was a Diplomate of the American Board of Pathology. He was a member of the Kiwanis Club, the Arizona Club, and the Phoenix Chamber of Commerce. Outside of his professional work, his interest was in quiet cultural pursuits, his home with its flowers and shrubbery, music and reading, and a citrus grove in which he took considerable pride.

It should be recorded that Dr Mills was known almost as well in the specialty of radiology as in that of pathology. While not a prolific writer, he did produce personally or in collaboration with others some eighteen published articles, which reflect his interest in the unusual and his careful study of useful clinical laboratory procedures.

His physical disability was cardiovascular, arising from an arteriosclerosis of obliterating type. He had suffered a sudden attack of Menier's disease with resulting deafness some years ago. Later a sudden paralysis of the left diaphragm developed, arteries in one or more fingers closed, causing painful Buerger's syndromes. A finger was amputated and histologic study revealed the characteristic endarteritis obliterans. Doubtless similar arterial occlusions brought on the final fatal illness, which culminated in decompensation and pulmonary edema.

Dr Mills won the respect of his wide circle of friends, this respect growing into an abiding affection on the part of those who were closely associated with him in professional work or social contacts. Through the years his poise and courtesy, his consideration for others, his attention to detail and his excellent judgment in his work, his cultural appreciation of music, art

and literature, marked him as a Christian gentleman, a scientist of no mean achievement, a sympathetic friend

Selected from an Obituary prepared by  
DR W WARNER WATKINS, F A C P , Phoenix

### DR FRANK GRAUER

Dr Frank Grauer, F A C P , one of the oldest active physicians in the City of New York, died in the Presbyterian Hospital of New York City of a coronary occlusion on February 16, 1945

Dr Grauer was born in New York, February 25, 1864, attended the College of the City of New York, and graduated from the Bellevue Hospital Medical College in 1884. During his early career he was assistant to the chair of pathological anatomy and medicine, and instructor in the Carnegie Laboratory of Bellevue Hospital Medical College, curator to Bellevue Hospital, pathologist to the Harlem, City, St John's Guild, and Park Hospitals, also, formerly physician and pathologist to the Lutheran Hospital of Manhattan. Following his graduation he did postgraduate work in the University of Berlin and in Frankfurt, Germany, and later studied at Harvard and Johns Hopkins.

Dr Grauer was held in very high regard as a doctor, and it is of interest to note that his Fellowship was sponsored by the late Drs Lewellys F Barker, Harold Brooks, and Joseph H Byrne who was Associate Secretary General of the College from 1918 to 1921. Dr Grauer continued to look after his practice until a short time before his death.

ASA L LINCOLN, M D , F A C P ,  
Governor for Eastern New York

### DR GUSTAV ADOLPH PUDOR

Dr Gustav Adolph Pudor, F A C P , Portland, Maine, died March 7, 1945. He was born in Portland, August 31, 1864. His father Dr Christian F Pudor died when the boy was barely 6 years old, and his education was guided by his mother. He attended the public schools and entered Harvard College, graduating with the degree of Bachelor of Arts in 1886 summa cum laude. He then entered Harvard Medical School and received his medical degree in 1889. Two years of study in Berlin University followed, where in the latter part he had a severe attack of the then rampant influenza which nearly cost him his life, as he insisted on continuing his studies until he broke down, and only complete and protracted rest in a quiet small town preserved his life. In 1890 the young doctor hung out his shingle at the door where his father's name had not been taken away in all these years after his death. Dr Pudor became city physician, holding the appointment for two years. In the meantime he had decided to go into the special field of dermatology, and in order to prepare himself fully he again went to Europe for study. He was greatly appreciated at the clinics in which he worked.

and received several offers to stay, but he declined. While in Germany he married Fraulein Margarete Besig, but as he wished first to become established in the then new field of dermatology, he returned to America alone, leaving his young bride to follow him later. His new work gradually started and succeeded. He was house doctor for a few years at the Maine School for the Deaf, and then was elected to the new chair of dermatology at the Bowdoin Medical School, an appointment he held until this department of Bowdoin College was closed for lack of funds. He gained the love and admiration of his students both for his excellent teaching and human and humorous approach.

During the first World War he served as Captain in the United States Army at a Base Hospital at Camp Devens, Massachusetts.

Dr Pudor was on the staff of the Maine General and Children's Hospitals until retired for age. The Venereal Disease Clinic of the Portland Dispensary was his special pet, and he devoted long years of intense work to it. In January, 1941, he suffered a second attack of influenza, which forced his retirement from practice, and he never regained full strength again. He had been a Fellow of the American College of Physicians since 1927, and during his active years thereafter he seldom missed any of its Annual Sessions.

Dr Pudor was more than a dermatologist. He was a lovable human being. To a remarkable degree he always displayed that old-fashioned courtesy which makes one shrink from ever uttering a word that might wound the feelings of a brother practitioner. He was a modest man who carried his honors lightly, an honest man who spoke candidly, a friendly man who really was interested in his neighbors, his associates, and his patients, a truly Christian gentleman, who without professing any particular piety, exemplified in his daily life his faith and convictions that "it is better to give than to receive." To quote Osler, Dr Pudor brought to the practice of medicine "the philosophy of hard work, the philosophy which insists that we are here, not to get all we can out of the life about us, but to see how much we can add to it."

For years I roomed with him as together we attended sessions of the American College of Physicians where, among a host of friends and acquaintances he was affectionately addressed as "Gus." Wherever we appeared there soon developed, through his charm of manner, his sincere cordiality, a camaraderie that was good to behold. Here was a nature "sloping toward the southern side," as Lowell put it, which made and kept friends. Early in life he learned that "temporal salvation depends on good food, abundant rest and cheerfulness." That he had attained in full measure. Ere this he must have heard the words, "good and faithful servant."

Selected from an Obituary in the  
Journal of the Maine Medical Association  
by E. W. GEHRING, M.D., F.A.C.P.,  
former Governor for Maine

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## HIRSUTISM IN FEMALES, A CLINICAL STUDY OF ITS ETIOLOGY, COURSE AND TREATMENT \*

By GROSVENOR W BISSELL, M D,† and ROBERT H WILLIAMS, M D,  
*Boston, Massachusetts*

THE bearded lady has always been a subject of lively interest. To the public she is amusing, to the showman profitable, to the physician physiologically fascinating—and to herself, utterly miserable. Many instances of virilized women may be found in the literature, most of whom have been suffering from adrenal, pituitary, or ovarian tumors. The earliest of these reports are little more than clinical observations, some with appended pathological findings. Later, improved chemical and biological technics often aided in discovering the site of the disturbance. In spite of our increased knowledge of endocrine physiology, however, much of the information is still conflicting and obscure.

Despite the voluminous literature concerning functional endocrine tumors, their actual occurrence is fairly rare. In contrast, the occurrence of hirsute women is common. In the past two years, we have seen more than 200 such patients. Most of them have come to us with complaints which were mainly cosmetic. As their histories were analyzed, however, the altered emotional state became a most striking feature. As a result of their masculine appearance, often in the presence of thoroughly feminine inclinations, many were pitiful neurotics.

In contrast with the many reports of masculinization resulting from functioning tumors, is the paucity of information regarding this type of "idiopathic" malady. We believe that this neglected type of hirsutism represents the most important variety of the disease, because of its much commoner occurrence. Accordingly, we decided to select at random a group of bearded women and to conduct certain investigations of their endocrine status. Only through numerous studies of this type will information be

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obtained sufficient to clarify the problem and to indicate a satisfactory method of therapy, which is so sorely needed

Before reporting our findings it may be well to consider briefly the subject of hair growth. A few pertinent experiments on animals demonstrate the following facts. Well-fed adrenalectomized rats<sup>1</sup> demonstrate precocious hair growth. Underfed normal rats have delayed growth of hair even when skeletal growth continues<sup>2</sup>. In these underfed animals the adrenals hypertrophy, and removal of these enlarged glands causes growth of new hair within 40 hours after adrenalectomy<sup>3</sup>. Administration of estrogens retards hair growth in rats,<sup>4</sup> guinea pigs<sup>5</sup> and dogs<sup>4</sup>. Concomitant administration of androgens prevents this effect in rats<sup>5</sup>. Gonadectomy in fowls often causes changes in plumage, which in birds is somewhat analogous to hair<sup>6</sup>. Pituitarectomy and thyroidectomy have been shown to exert influence upon the pilary system of various animals.

Important as is this work in demonstrating some degree of hormonal control on mammalian hair growth, most of it is not applicable to man whose pilary system is unique in several ways. The most obvious sign of this dissimilarity is the marked difference in hair development on contiguous body areas in man. Thus any discussion of human hair growth should include consideration of (1) hair growth per se, and (2) possible secondary influences. Much of the work on the first subject has been performed, and recently reviewed by Danforth<sup>7</sup>. He states that although humoral control of human hair growth probably exists, the final product of each individual follicle is largely determined by constitutional factors within the hair cell itself. Thus, considering the humoral complexes of the male as one factor, and of the female as another, there are some follicles unaffected by the difference, while in others the effect may range from slight to profound. In other words, there is a constitutional gradient of response of each individual follicle to the hormonal influences which are presumed to be equally accessible to all. This might explain why two morphologically identical follicles may produce fine body hair until puberty, when the product of one changes to long terminal hair, while the product of the other continues unchanged throughout life.

On the basis of this concept, Danforth<sup>7</sup> offers the following classification of hair. *First, general body hair* ("lanugo" or "vellus"), which is uninfluenced by endocrine factors. *Secondly, ambosexual hair*, present in males and females, but dependent on hormonal stimulation which is apparently equivalent in both sexes. The axillary and pubic hair exemplify this type. *Thirdly, truly sexual hair*, represented by the beard of the male, and less clearly by the terminal hair of the shoulders, anterior chest and abdomen. The head hair, or *capitus*, is probably a secondary sexual characteristic also, since its weight per unit of length is greater in males<sup>8</sup>.

The adrenal cortex, gonads, thyroid and anterior pituitary are the endocrine glands mainly concerned with hair production. The influence of the adrenal cortex on female ambosexual hair growth has recently been empha-

sized.<sup>9</sup> In pan-hypopituitarism and in Addison's disease, conditions in which the adrenal cortex is virtually non-functioning, axillary and pubic hair is absent. The adrenal cortex in hypo-ovarian dwarfs, although present, is of subnormal size, likewise, the axillary and pubic hair is present but diminished in amount. The ovaries and anterior pituitary apparently exert no direct influence on ambosexual hair growth in the female. This is proved by cases of Addison's disease with adequate ovarian and anterior pituitary function,<sup>9,10</sup> which never developed pubic or axillary hair. The maintenance of ambosexual hair after the menopause is also an indication of the absence of ovarian influence. Prepubertal ovariectomy results in absent axillary and pubic hair but this is probably due to secondary lack of stimulation of the adrenal cortex by estrin.<sup>9,11</sup>

In the male, there may be more complicated factors influencing the growth of ambosexual hair. Males with panhypopituitarism, and thus, secondary adrenal cortical and gonadal hypofunction, have little or no axillary or pubic hair. Men with Addison's disease have sparse pubic and axillary hair. Prepubertal castration does not prevent the appearance of ambosexual hair, although it may not be abundant.<sup>12</sup> Testosterone has been found to increase the size and number of the pubic sebaceous glands in prepubertal boys.<sup>13</sup> It would appear that male ambosexual hair growth is apparently conditioned by a synergism between the gonads and adrenals.

The beard of the male would seem to be influenced chiefly by testicular secretions. Supporting this assumption is the absence of the beard in prepubertal castrates and its disappearance following postpubertal castration. Hypopituitary males, who have secondary hypogonadism, likewise have no beard. Men suffering from Addison's disease do not experience such loss.

The ambosexual hair in both sexes, and the beard in males, are diminished or absent in myxedema. This may be due in part to the secondary hypogonadism known to accompany this disease.<sup>14</sup> The major cause, however, is probably the generalized hypometabolism which affects not only the individual follicle growth, but also the function of the other endocrine glands.

Although the general body hair is supposedly uninfluenced by endocrine factors,<sup>7</sup> clinical observation would seem to indicate that this is not entirely true. One of the characteristic features of patients suffering from pan-hypopituitarism is the virtual absence of body hair. Some cases of Addison's disease have scanty or absent body hair. Individuals with anterior pituitary hyperfunction are frequently hairy. Patients who have had ovarian and adrenal tumors removed<sup>15,16</sup> frequently demonstrate postoperative diminution of their body hair. It would seem that under certain circumstances even the *vellus* is conditioned by endocrine stimulation. These effects may, of course, be mere reflections of a generally altered metabolism.

The foregoing facts seem to indicate that there are two major influences on hair growth, one constitutional, the other humoral. The *constitutional factor* is the capability of response of each individual follicle to endocrine stimuli. The *humoral factor* represents the various hormones supplying the



stimulus for hair production to those follicles inherently sensitive to their action. Other local factors, such as follicular nutrition, nerve and blood supply must also exert their effect.

Since the control of normal hair growth is still obscure any discussion of the causes of pathological hair growth is difficult. Hirsutism is defined as excessive hair growth, but there is no clearcut distinction as to what type of hair is involved. Also, there is a tremendous variation in the quantity and distribution of body hair in normal subjects. Danforth's studies<sup>17</sup> indicate that about one-third of the apparently normal white females have hypertrichosis. Redlich<sup>18</sup> has classified hair distribution in the male, but he included only body-hair patterns, which are presumably less affected by endocrine factors.

Although lacking in precise definition, hirsutism has been reported with many pathological entities. The best recognized of these are basophilic tumors of the anterior pituitary (Cushing's disease) and neoplasm and hyperplasia of the adrenal cortex (adrenocortical syndrome, adrenogenital syndrome, or Cushing's syndrome). Also associated with hirsutism are arrhenoblastomata of the ovary,<sup>19</sup> thymic tumors (with secondary adrenal hyperplasia),<sup>20, 21</sup> lutein cell tumors,<sup>22</sup> and diffuse luteinization of the ovaries.<sup>23</sup> Schwartz<sup>24</sup> quotes some of the continental literature reporting hirsutism associated with teratoma, neuritis, mumps, and encephalitis. It has been described not infrequently accompanying low mentality states, and multiple sclerosis.

Permanent hirsutism may also accompany certain physiological processes. It may accompany or immediately follow menarche, childbirth or menopause. Genetics may also influence hair growth. Some families may be hirsute almost from birth. Likewise, certain races, notably the Jews and Italians, appear particularly affected. Hirsutism may also be transient. It may accompany pregnancy and disappear postpartum. Recently we have noted its occurrence in two cases of severe burns. It may also appear during therapy with dilantin<sup>25</sup> and testosterone.<sup>26</sup>

It may be seen that *hirsutism* is a malady of unclear definition, and complex etiology. In this paper, for purposes of clarity, we shall confine our discussion to female hirsutism, which will connote the presence of a beard, associated with altered ambosexual hair-growth, unless otherwise stated. Much of the current opinion seems to consider adrenal cortical malfunction as the greatest single factor concerned in the hirsute syndromes. Our observations were made with this premise in mind.

#### CLINICAL MATERIAL

Thirty-three patients have been observed during a period of three years. Actually, we encountered scores of patients during that time, but many were unwilling to permit adequate study, or did not satisfy the above criteria of hirsutism.

When first seen, the patients ranged from 19 to 67 years of age. Twenty-two of the group were married and the majority were hirsute before their marriage. Most of the group were brunette and tended to be swarthy. One patient, however, was a light blonde (I K) and her abnormal hair was of the same hue. There were six Jews and five Italians. One patient (P W) was a negress, which is interesting in the light of a recent article which states that hirsutism does not exist in this race<sup>21</sup>.

Since hirsutism occurs either in the presence of some pathologic lesion, or as an abnormal response during some physiological state, we employed the following classification in cataloging our patients:

I *Permanent Hirsutism*

- A Pituitary
- B Adrenal cortex
- C Gonads
- D Hypothalamus
- E Other lesions (pinealoma, thymoma, etc.)
- F Idiopathic\*
  - 1 Postpubertal
  - 2 Postpregnancy
  - 3 Postmenopausal
  - 4 Genetic
    - a Familial
    - b Racial
  - 5 Unclassified

s

II *Transient Hirsutism*

- Pregnancy
- Therapeutic
- Other causes (burns, etc.)

In our series of 33 patients, 29 fall into "the idiopathic" class. Of these, 20 are of the postmenarcheal type, four postpregnancy, two postmenopausal, two familial, and one unclassified. Four additional patients (one pseudohermaphrodite, one acromegalic, and two cases of transient hirsutism) are discussed separately.

*"Idiopathic" Hirsutism* Twenty-four of these 29 women had heavy beards, which required daily shaving (figure 1). All but four of these displayed marked hypertrichosis on other parts of the body (figure 2). The abnormal hair was coarse and wiry. The majority had increased hair over the forearms and thighs, usually an increase over the shoulders, and occasionally about the nipples and between the breasts. In 23 subjects the pubic hair distribution was distinctly male. One patient (F M) had auburn head, pubic and axillary hair. Soon after puberty she developed an extension of her pubic hair over her abdomen. Two distinct abdominal triangles with opposing bases resulted, one of auburn hair, representing the original

\* "Idiopathic" is used in this paper to denote cases in which the primary etiologic factor causing the hirsutism was not clearly demonstrable. Undoubtedly some of these cases might be classified as adrenogenital syndrome, etc., but the authors prefer to consider them in a less confining category, until better diagnostic proof is established.

normal female distribution, and the other of black hair, indicating the more recently acquired male escutcheon!

Two of our patients, each Italian, were excellent examples of familial hirsutism. One (A M) had three hairy sisters, a hirsute mother and grandmother. She had heavy facial hair, male pubic hair distribution, and marked increase in hair over her extremities and shoulders. The other patient (L M) had five daughters and several granddaughters who showed marked generalized hirsutism. Even the five year old granddaughter of this patient had a well-defined moustache and beginning facial hirsutism.



FIG 1 (Case L T) This patient's beard is the result of not having shaved for about 48 hours. Note the acne and seborrhea of the skin.

None, however, displayed male pubic hair. In both of these families the hair tended to be more silky and finer in texture than in the patients with other types of hypertrichosis. It was similar to excess "lanugo" hair described in the famous Jefticheff and Schwe Maong families of "dog men" <sup>17</sup>.

Two patients were representatives of the postmenopausal type. Both had typical sparse, long, curly chin hair and well-marked moustaches. Otherwise their body hair was normal.

Two patients (M J and M M) displayed moustaches only, unassociated with abnormal body hair. They were included because of the large number of women seen with this type of abnormality.

*Signs and Symptoms Related to the Sexual System* Aberration in sexual structure and function is an integral part of hyperadrenocorticism. In Cushing's syndrome, there is presumably an overproduction of steroids concerned chiefly with gluconeogenesis, with little involvement of the androgenic components of the cortex <sup>27 28</sup>. It is classically associated with weakness, genital and breast atrophy, and sexual underfunction. The adreno-

genital syndrome involves an overproduction of androgenic, anabolic factors, and is associated with increased strength, good musculature, and genital hypertrophy

•The effects of androgenic overproduction depend upon the time of its occurrence. If the process begins in utero, pseudohermaphroditism results



FIG 2 (Case S. L.) Typical patient with "idiopathic" hirsutism. Note the male pubic hair distribution and the hirsutism of the face and extremities. The breasts are hypertrophied.

if it is delayed until sexual maturity is attained, the adrenogenital syndrome ensues. An enlarged clitoris is one of the classic signs of this latter disease. Formerly<sup>29</sup> it was considered one of the diagnostic criteria, but recently it has been pointed out that there may be a great overlapping of signs, many cases of Cushing's syndrome displaying features of the adrenogenital syndrome and vice versa.<sup>30</sup>

The clitoris was definitely enlarged in 11 of these patients. In each there was also a male configuration of pubic hair. They were among the most bearded of the group. It is of interest to note that in our series, although a male pattern of pubic hair distribution sometimes occurred without clitoral enlargement, the reverse was not encountered.

In 15 patients the labia majora were hypertrophied, giving a pouting, or ballooned appearance. This was usually accompanied by clitoral hypertrophy, but in a few patients (S DeA, L S, S L, G K, M J) it appeared to be the only abnormality of the external genitalia. Two (S DeA and S D) had infantilism of the internal pelvic structures. Another (L T) was found to have atrophic ovaries at operation. The rest had apparently normal internal pelvic organs.

In these 29 patients menstruation was normal in 16, and irregular in 12, often with six-month intervals between periods. One patient (S DeA) had never menstruated. Four of the 11 patients with clitoral enlargement had perfectly normal periods. Libido was low or absent in 12 patients, apparently normal in the remainder.

The breasts were well-developed in 27 patients, in fact, there was a tendency toward increased development. This is of interest inasmuch as the adrenocortical syndromes are associated with lack of breast development, or breast atrophy.

*Other Physical Findings* Obesity is a counterpart of adrenal cortical hyperfunction, especially the Cushing syndrome. Recently, however, it has been emphasized that this obesity is not extreme and may be merely a redistribution of fat, which may give a superficial appearance of obesity<sup>31</sup>. The actual weight of children with adrenocortical obesity is not greatly increased over the average<sup>32</sup>. That adrenal cortical "obesity" is actually fat and not merely tissue fluid is recently reported<sup>33</sup>.

In our group, obesity was generally characteristic. Only seven patients were thin. By comparing the actual weight with the ideal weight of each patient for her height and age, it was found that there was an actual increase in weight present (chart 1).

The fat in our patients was largely confined to the trunk. The arms and legs were inclined to be normal or even slender. Most of the group had broad faces, thick necks and heavy shoulders. Usually the abdominal fat panniculus was increased, and the hips broad and fat. In none was the fat painful to pressure. The obesity did not seem refractory to weight reduction.

*Thin skin* with prominent veins has been noted in Cushing's syndrome. Although an occasional patient demonstrated prominent venous patterns over the breasts, only one (E M) had an integument of the type seen in Cushing's syndrome, she showed many other manifestations of this syndrome. It is often assumed that acne is related to excessive androgen formation<sup>34</sup> and acneiform lesions are frequently described with Cushing's syndrome. Marked acne was observed in five of this group, slight acne in two others.

It is of interest that the two patients with most severe acne had the least concomitant virilism (K C, R M)

*Reddish-purple striae* on the abdomen and shoulders were noted in seven patients. Eight of the group complained of the appearance of ecchymoses upon relatively slight trauma.

Benign hypertension was found in six patients, all of whom were over 42 years of age.

*Results of Sugar Tolerance Tests* Mild diabetes is one of the features of certain types of increased adrenal cortical function. It has been shown that some of the cortical hormones promote gluconeogenesis<sup>34</sup>. Since there is thought to be excessive production of such adrenal cortical hormones in Cushing's syndrome, the diabetes accompanying that disease has been attributed to the increase in gluconeogenesis coupled with an inhibition of the tissue anabolism<sup>27, 28</sup>.

The diabetes of hyperadrenalcorticism is insulin-resistant. Recently, Fraser, et al<sup>36</sup> have devised a glucose and insulin tolerance test, based on tests developed by Himsworth<sup>37</sup>. The procedure consists of the simultaneous oral administration of glucose, with sufficient insulin given intravenously to insure its utilization. The resulting blood sugar curve, taken at 30-minute intervals, is essentially a straight line in normals and in insulin-sensitive diabetics. In individuals with insulin insensitivity, there is a rise in the blood sugar level simulating a diabetic type of oral glucose tolerance curve. This test has been found positive in cases of Cushing's disease<sup>36, 38</sup>.

The test was performed on all of our cases by administering to each, in a fasting state, 100 grams of glucose by mouth, followed immediately by the intravenous injection of regular insulin (0.1 unit per kilogram of body weight). (This is the technic advised by Fraser except that four blood specimens were taken at 30-minute intervals, after the fasting specimen.) Since the test may be influenced by the preceding diet,<sup>39</sup> each patient had taken a high carbohydrate diet for at least three days before the procedure.

Five of our patients had classical diabetes mellitus. All were insulin-insensitive as measured by the foregoing test. Fourteen of the remaining 24 showed abnormal glucose-insulin tolerance curves (figure 3). It may be seen that in all patients the blood sugar level at 60 minutes was well above the fasting level and in most had not yet returned to the fasting value at the end of two hours. All of the patients except one (M L) were obese. Of the normal curves obtained, two patients were very slender, and the rest somewhat overweight but not to the degree of the foregoing group.

The greater frequency of abnormal glucose and insulin tolerance tests in the obese hirsute women led to the performance of similar tests on patients who were merely obese. Three men, weighing 205, 263, and 286 pounds, and two women weighing 180 and 175 pounds, were studied. None exhibited abnormal hair growth or had any symptoms or signs referable to hyperadrenocorticism. All of these patients also had abnormal glucose insulin tolerance curves (figure 3).



CHART I—Continued

Number	Initials	Age	Married	Actual Wgt	Ideal Wgt	Height	Onset Disease	Catamenia				Hirsutism							Large Breasts	Obesity	Early Strength	Later Weakness	Acne	Striae	Prominent Veins	Bruisability	Glycosuria	Renal Stones	Hypertension	17 ketosteroids mg /24 hours	
								Normal	Amenorrhoea	Irregular	Menopause	Libido	Pregnancies	Face	Arms Legs	Male Pubic Escutcheon	Clitoris	Hypertrophied Labia													
Post-Pregnancy Hirsutism																															
21	D N	27	+	197	129	64	25	+	—	—	+	+	—	N	+	+	+	+	+	+	+	+	+	+	+	+	+	0	27		
22	J McD	34	+	137	121	60	31	+	+	+	—	—	—	N	+	+	+	+	+	+	+	+	+	+	+	+	+	0	112		
23	E M	42	+	164	128	60	32	+	+	+	—	—	—	N	+	+	+	+	+	+	+	+	+	+	+	+	+	0	240		
24	M J	45	+	242	141	64	41	+	—	—	+	+	—	N	+	+	+	+	+	+	+	+	+	+	+	+	+	0	143		
																													56		
Post-Menopausal Hirsutism																															
25	G L	67	+	182	152	66	47	+	—	—	+	+	—	L	+	+	+	+	+	+	+	+	+	+	+	+	+	0	02		
26	A McG	51	+	169	138	62	35	+	—	—	+	+	—	L	+	+	+	+	+	+	+	+	+	+	+	+	+	0	28		
Familial Hirsutism																															
27	L M	61	+	168	140	63	B	+	—	—	+	+	—	N	+	+	+	+	+	+	+	+	+	+	+	+	+	0	18		
28	A M	23	+	221	121	61	B	+	—	—	+	+	—	N	+	+	+	+	+	+	+	+	+	+	+	+	+	0	05		
Unclassified																															
29	L T	33	+	135	133	64	25	—	—	—	—	—	—	L	0	+	—	+	+	0	+	+	+	+	0	0	0	0	120		
																													68		

Key N=Normal, B=Birth, L=Low, O=Absent



We attempted to improve the test by giving both the glucose and insulin intravenously, using 25 grams of glucose in a 50 per cent solution<sup>40</sup> and 0.1 unit of regular insulin per kilogram, of ideal body weight. The results obtained in a few cases showed very inconstant responses, but there was no evidence of insulin insensitivity.

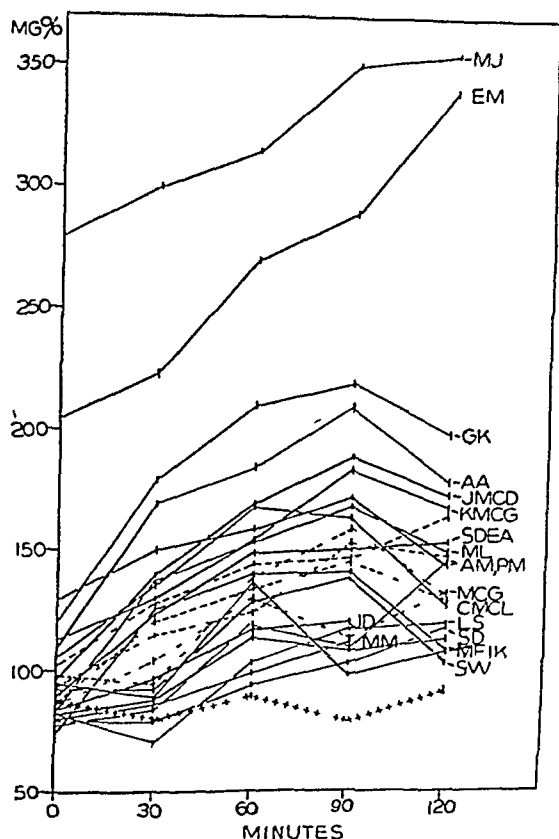


FIG 3 Glucose and insulin curves of patients showing tendency towards insulin resistance ++++ Normal curve ——— Hirsute patients - - - - Obese patients without hirsutism

An evaluation of the glucose-insulin tolerance test as a clinical procedure is not pertinent to the general subject under consideration. However, the possibility of the test being abnormal in some cases of simple obesity should be remembered. Since obesity is present in Cushing's syndrome, and since Himsworth and Kerr<sup>38</sup> have pointed out that "the insulin-insensitive diabetics tend to be older, obese" it may be asked if the abnormal curves obtained were not conditioned somewhat by the presence of overweight.

**17-ketosteroids** The urinary 17-ketosteroids are (by definition) those steroids possessing a methylene and a ketone group at the seventeenth carbon atom which enables them to combine with meta-dinitro-benzene (in the presence of alkali) to produce a pink color. In the female it is believed

that all of the 17-ketosteroids are produced by the adrenal cortex. Their determination would seem to furnish an index of adrenal cortical function in the female.

The 17-ketosteroid which represents the urinary end products of androgen metabolism are found in the neutral (non-phenolic) fraction of hydrolyzed urine. Estrone, also a 17-ketosteroid, is removed with the phenolic and the acid fractions, by treatment with alkali. The remaining material represents the alcoholic alpha and beta ketosteroids, and a non-alcoholic fraction. The beta ketosteroids are precipitated by digitonin which gives a means of separation. The total and alpha ketosteroids are increased in cases of adrenal hyperplasia and adrenal cancer<sup>41, 42, 48</sup>. It is believed that the beta and non-alcoholic fractions are elevated only in cases

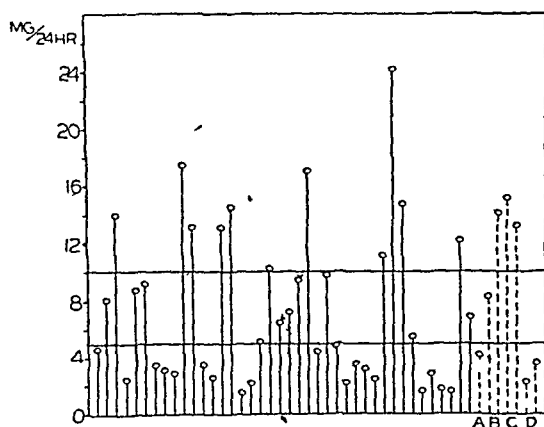


FIG 4 17-ketosteroid excretions in cases of hirsutism. A—Acromegalic B—Pseudohermaphrodite C, D—Transient hirsutism of pregnancy. The rest are cases of "idiopathic" hirsutism.

of carcinoma of the adrenal cortex<sup>42, 48</sup>. The 17-ketosteroids were determined in our cases according to methods which have been employed in this laboratory for several years<sup>41, 44</sup>. In some instances, alpha fractions were determined, so that an estimate of the beta and non-alcoholic fractions might be obtained. The latter were not further separated. In this laboratory, the normal range of excretion of total ketosteroids in adult females is from 5 to 10 mg per 24 hours. Collections were always made when the patients were in excellent health and free of the most trivial infections, since even mild infectious states are known to lower steroid output. It will be noted that the great majority of these patients had 24-hour 17-ketosteroid excretions within the normal range, or in a range considered definitely subnormal for adult women (figure 4). This latter finding has surprised us considerably, and we are unable to explain it. Somewhat high values were found in four patients (E M, M L, L T, and S D) all of whom showed severe virilizations. Three patients (I K, M F and F M) also exhibited slightly elevated values. The first two of these exhibited hypertrophy of

the clitoris The third patient was slim, and although she had a male hair distribution, complained only of infrequent menses In a few cases in which beta fractions were obtained, the results were normal

*Radiographic Studies* Roentgenograms of the skull, sella, spine, pelvis, and long bones were obtained in each case In each, the sella turcica was normal No abnormalities were detected in the long bones, or epiphyses Two patients showed slight osteoporosis of the spine One of these (A McG) probably had postmenopausal osteoporosis, while the other patient (E M) had Cushing's syndrome The latter patient also showed slight decalcification of the skull

All patients had flat films of the abdomen for kidney outline and position If any displacement was noted, intravenous or retrograde pyelography was then employed In none was there any finding suspicious of adrenal tumor or hyperplasia Two (M L, M Me) showed the presence of renal calculi, the first, bilateral, the second, unilateral In both, pyelotomy was performed because of renal colic We did not feel that perirenal air injections for roentgenographic studies were justified in most of these cases

*Other Laboratory Data* Fourteen of this group had one or more basal metabolic rate determinations, all within normal limits Qualitative tests of the urine (Sulkowitch test) showed no evidence of hypercalcinuria save in one case (M L) Red blood cell counts and hemoglobin determinations gave no evidence of polycythemia In seven of the more severe cases, estimations of sodium, potassium, chloride and  $\text{CO}_2$  were performed, but no deviation from the normal was observed

Estimations of gonadotropins were made in several cases It is interesting that in two instances (P W, G K), although the patients were still menstruating, assays of the urine for the follicle stimulating hormone showed that more than 10 rat units were excreted per 24 hours, indicating hyperfunction of the pituitary gland Roentgen-rays of the sella turcica were normal in both instances

As we mentioned above, most of the cases came to us with complaints chiefly related to the disturbing cosmetic or psychic effects of hirsutism Three patients, however, seemed to represent classical adrenal cortical syndromes Their histories are given in detail Some of the many problems involved in the establishment of an etiology of hirsutism and the difficulties encountered in the treatment of these individuals are illustrated in the following cases

#### CASE REPORTS

*Case 1* M L, a 19 year old student nurse, was admitted to the hospital May 27, 1941, because of a typical attack of renal colic on the left At the age of 12 she began to have painless menstrual periods of eight days' duration occurring at intervals of two to four months For five months before this hospitalization she had had no menses At 17 she noticed an abnormally large amount of hair on her face, abdomen, arms and legs Soon it became necessary for her to shave daily She

presented a striking configuration (figure 5) in that she had a large head and neck, broad shoulders, and narrow hips. The excess adipose tissue in the head and neck stood out in great contrast to very small amounts elsewhere. The breasts were rela-

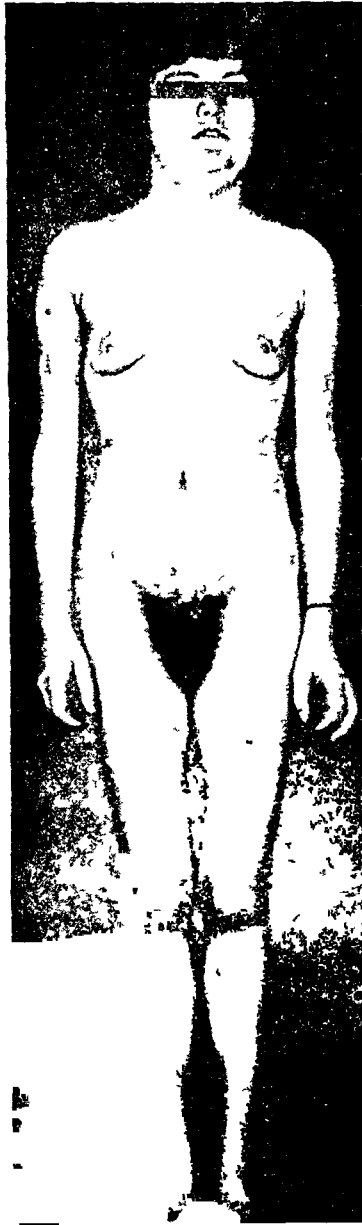


FIG 5 (Case M. L.) Note the large head and neck, broad shoulders, narrow hips, small breasts, male escutcheon, and prominent muscles

tively small. Many muscle patterns in the extremities were readily noticeable. She weighed 137 pounds and was 68 inches tall. There were patches of brown pigment over the chin, neck, axillae, areolae, breasts and abdomen. A heavy beard was present and there was a moderate increase of coarse black hair over shoulders, extremities,

and abdomen. A male escutcheon was noted. There were no striae. Acne was not present. The blood pressure was normal. The labia majora were distinctly large and pouty and the clitoris was twice normal size. The uterus and ovaries seemed to be normal.

Red, white and differential blood cell counts were normal. The urine contained a small number of red and white blood cells but no albumin or sugar. *B. coli* were cultured from the urine. The Sulkowitch test for calcium gave a strong reaction even after the patient's diet had contained only a small amount of calcium for three days. Blood chemical studies showed the sodium to be 141 m eq per liter, potassium 4.5 m eq per liter, non-protein nitrogen 34 mg per 100 c c, calcium 10.2 mg per 100 c c, phosphorus 3.8 mg per 100 c c, phosphatase 3.4 Bodansky units, cholesterol 154 mg per 100 c c and total protein 7.1 gm per 100 c c. Roentgenograms of the sella turcica, chest, hands, humeri, femora, and pelvis were normal. The development of the bones was in accordance with the age of the patient. Pyelograms showed two small calculi in the left renal pelvis, and a small one in the right renal pelvis, but no displacement of either kidney.

The glucose-insulin tolerance test, using 6 units of insulin intravenously and 65 grams of glucose by mouth, gave the following changes in blood sugar: 87, 119, 133, 143, 142, 143, and 147 mg per 100 c c, the specimens having been taken at 0, 20, 30, 45, 60, 90, and 120 minutes after beginning the test. The basal metabolic rate was plus 2 per cent. The visual fields were normal. An assay of a 24-hour specimen of urine for 10 rat units of follicle stimulating hormone was negative. The excretion of 17-ketosteroids was found to be 7.4 and 10.3 mg during two periods of 24 hours. In the latter specimen 10.1 mg of the alpha fraction were present. Stained smears of vaginal scrapings taken at intervals showed an estrin effect but never a luteal effect.

On July 21 a left pyelolithotomy was performed. The left adrenal was found to be somewhat enlarged and about one-half of it was removed. Cut section showed the center to be thicker than normal and fat stains revealed an excessive quantity of lipid. Within a week after operation the patient had her first menstrual period in six months. The flow lasted for seven days and was associated with cramps, suggesting that a secretory endometrium was present. An endometrial biopsy obtained one day before the next period, one month later, demonstrated a secretory endometrium. Following operation no change in the hair growth was noted, but there was a slight increase in breast development. There were 13.4 mg of 17-ketosteroids, 10.1 in the alpha fraction, excreted on August 22, and the total excretion on August 30 was 6.8 mg. The serum sodium and potassium remained normal.

The foregoing data indicate that following the operation an improvement of the patient resulted in some respects, but there was no change in the hirsutism, the greatest concern of the patient. By this time we had some evidence that the patient was suffering from hyperadrenocorticism which presumably had resulted from the excessive production of adrenotropic hormone. Experience has illustrated that in patients with disorders of the type encountered here, neither roentgenotherapy nor surgery directed toward the adrenals or pituitary has been of much aid. Thereupon, we attempted to produce an "antihormone effect" by the prolonged administration of adrenotropic hormone. Such an approach is based on the hypothesis that injections of this hormone during a period of a few weeks would bring about changes in the body, immune or otherwise, which would prevent the adrenals from responding appreciably to either the injected hormone or the patient's own adrenotropic hormone and might thereby cause a regression of the disease. On September 3 she began receiving subcutaneous injections of adrenotropic hormone\* 1 c c daily. Five days

\* We are indebted to the Armour Laboratories, Chicago, Ill., for Adrenotropic Factor. The solution used contained 10 adrenotropic units (Collip) per 10 c c.

later the dosage was increased to 1 cc twice daily, and this was continued until October 9. During the course of treatment the only clinical change observed was that the patient developed an increased desire for salt and complained of slight sensitivity to cold. On September 14 the excretion of 17-ketosteroids was 7.0 mg, 6.6 mg of which was in the alpha fraction, October 5 the excretion was 13.3 mg with 11.2 mg in the alpha fraction. No change occurred in the serum sodium or potassium. At the end of the adrenotropin therapy a precipitin test was performed using the patient's serum and a specimen of the hormone used. A negative reaction was obtained even at 1:8 dilution and in spite of using a suspension of celloidin particles to increase the sensitivity of the test.

For two months after the adrenotropin therapy no treatment was given. During this time the patient's clinical status remained unchanged. The serum sodium and potassium remained normal. On October 28 a glucose-insulin tolerance test, using 65 grams of glucose, orally, and 65 units of insulin, intravenously, yielded evidence of insulin resistance as indicated by the following changes in blood sugar, expressed as milligrams per 100 cc of blood: 84, 105, 137, 151, 171, and 154, the specimens having been obtained at 0, 20, 30, 45, 60 and 120 minutes after the test was begun. Urine specimens saved over a period of four days (December 13-17) contained an average of 12.5 mg of 17-ketosteroids per day. Thus it would seem that the adrenotropin therapy had afforded no definite benefit.

We next considered the possible effects of the administration of ovarian hormones in large doses. It has been shown<sup>45, 46</sup> that in rats very large doses of progesterone cause atrophy of the adrenal cortex. Certain observations have been made<sup>47</sup> which indicate that estrin stimulates the production of the luteinizing hormone in the pituitary gland and this substance can stimulate the adrenal cortex causing it to secrete androgenic hormone. Accentuation of this process, as by the administration of large amounts of estrogens, would tend to increase the androgenic manifestations. However, estrogens also exhibit a directly antagonistic action to therapy with androgens. Whereas it is desirable to obtain the latter effect in hirsutism the former (masculinizing) effect would, of course, be undesirable. With these principles in mind we treated our patient with a large amount of progesterone,\* 25 mg intramuscularly daily, for two months, during the last month of which 1.66 mg of alpha estradiol benzoate was given intramuscularly three times weekly. During this therapy, in addition to studying the patient's clinical status, we also conducted balance studies, as concerned nitrogen, sodium, potassium and calcium (figure 6).

During treatment a definite enlargement of the breasts and hips resulted, but there was no change in the hirsutism. The progesterone therapy given alone or in conjunction with alpha estradiol benzoate had no definite effect on the nitrogen, sodium, potassium or calcium balances. The patient tended to remain in a slightly negative nitrogen balance. The calcium balance, although variable, tended to be negative most of the time. The serum calcium, sodium and potassium, determined twice during the course of therapy, remained normal. The excretion of 17-ketosteroids was less (average of 5.1 mg daily for four days) at the completion of therapy than had been found at any other time. However, a determination of the 17-ketosteroids one month later showed a return to the previous high level.

During the fifteenth four-day period of the balance study the patient developed an attack of renal colic on the right, and passed a small stone in the urine. A roentgenogram of the abdomen showed several small stones in the right kidney. On March 29, 1942, the right adrenal and kidney were explored surgically. Each looked normal, but about one-third of the adrenal was removed. On microscopic examination this tissue showed many areas of tuberculosis, some of which were caseous. The

\* We are very grateful to Schering Corporation, Bloomfield, N. J., for a supply of progesterone and alpha estradiol benzoate.

adrenal tissue otherwise appeared normal. A tuberculous sinus developed at the operative site and required several months to heal.

On July 17, 1942, the 17-ketosteroid excretion was 163 mg. It is to be emphasized that this was one of the highest values obtained in this case and was determined after the patient had been in bed several months with a chronic infection—factors which tend to lower the 17-ketosteroid excretion. On December 6 and December 30 she excreted 1.9 and 4.3 mg of 17-ketosteroids, respectively.

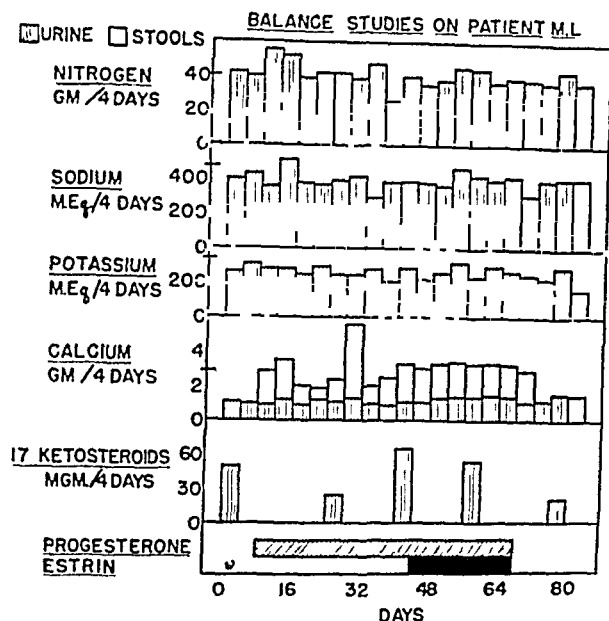


FIG 6 (Case M L) Each column is for a period of 4 days. The transverse lines on the ordinate represent the content of the various substances in the diet. The progesterone was given intramuscularly in doses of 25 mg daily. The estrin (alpha estradiol benzoate) was given, intramuscularly, in doses of 1.66 mg three times per week.

**Case 2** L T, a 33 year old married white woman was admitted to the Fourth Surgical Service of the Boston City Hospital on April 26, 1942, complaining of right upper quadrant pain and increased hair growth on her face and body. Physical examination revealed an obese, hirsute woman with vague abdominal tenderness. Laboratory examinations were within normal limits. The 17-ketosteroid estimation was 12 mg per 24 hours. Intravenous pyelograms showed partial fixation of the left kidney, perirenal insufflations were not conclusive but it was thought that there was enlargement of the left adrenal. She was discharged without further study.

She was admitted to the Medical Wards of the Massachusetts Memorial Hospitals on March 18, 1943, complaining of a progression of her hirsutism. She stated that she had gained 20 pounds in weight in the past three years, and had noted a definite increase in strength. Her voice had grown deep and had "cracked" several times while singing. Her skin had become increasingly greasy, acne had been present for eight or nine months, and some purplish-red striae had appeared over her arms and shoulders. Her face had become broad. Her catamenia had begun in her teens and had been regular until about one year previously. During the year preceding this hospitalization her periods were often seven to eight weeks apart and lasted for intervals varying from three to seven days.

Physical examination revealed an obese white female with a florid complexion, and a prominent beard and moustache (figure 1). The temperature was 98.6° F,

pulse 80 per minute, respiratory rate 18 per minute, and blood pressure 120 mm Hg systolic and 92 mm Hg diastolic. The skin was moist and pink, striae were present over the deltoid region and abdomen, acne was marked, especially on the face. The hair was increased greatly on the face, forearms, legs, and around the nipples. The pubic hair followed a male pattern. The visual fields were normal. The thyroid gland was normal in size. The heart and lungs were normal. There was slight tenderness of the right kidney where it was thought there was a palpable mass. Pelvic examination revealed normal labiae, a normal clitoris and a retroverted uterus. The neurological status was normal.

The red, white and differential blood cell counts and urinalyses were normal. The non-protein nitrogen was 22 mg per 100 cc of blood, fasting blood sugar, 73 mg per 100 cc, chloride, 103.4 m eq per liter,  $\text{CO}_2$  combining power, 59 vols per cent, and the creatinine was 2.1 mg per 100 cc. The oral glucose tolerance test yielded blood sugar values of 72, 126, 91, 66 mg per 100 cc, the samples having been taken at 0, 30, 60, and 120 minute intervals. The glucose-insulin tolerance test showed values of 76, 66, 86, 104 and 99 mg per 100 cc, the samples having been taken at 0, 30, 60, 90 and 120 minute intervals. Roentgen-rays of the skull, sella turcica, chest, and thymus were normal. Intravenous pyelograms were apparently normal. The spine showed some scoliosis in the dorsal region with slight decalcification. A 24-hour specimen of urine gave a negative assay for 10 rat units of follicle stimulating hormone. There were 12 mg of 17-ketosteroids excreted in the urine in 24 hours. The perimetric fields were normal.

Because of the sudden progressive nature of her symptoms and the questionable enlargement of the left adrenal suggested by perirenal insufflation, the patient underwent an exploratory laparotomy on April 14, 1943. At operation, an abnormal mass was thought to exist at the upper pole of the left kidney. The right adrenal was not enlarged. Both ovaries were small and atrophic. The uterus was slightly enlarged and contained fibroids. On June 6, 1943, a left adrenalectomy was performed. Although at operation the left adrenal gland was thought to be somewhat enlarged, the pathological report was "histologically normal adrenal."

She was discharged on June 19, 1943. Soon after her operation the patient stated that she felt weaker, and also that her beard required less attention. She lost 30 pounds and her periods were reestablished at monthly intervals. Despite her statements, we have observed no effect on her hirsutism.

*Case 3* E. M.,\* a 42 year old white female, was admitted to the Thorndike Ward on August 20, 1943, complaining of uncontrolled diabetes for some years, increased facial hair, and pain in the back.

Menarche occurred at 11 years and menstruation was often grossly irregular. She successfully underwent seven pregnancies, the last at the age of 32 years. Ten years previous to admission (almost immediately after her last delivery) she noted the onset of polyuria and polydipsia. At this time glycosuria was discovered. She continued to lactate for several years and noted the growth of a heavy black beard, which progressed to date and which required daily shaving. The hair of her head had thinned. The patient had been obese for about 15 years, her greatest weight being 225 pounds.

About nine years before admission she was operated upon for an ovarian cyst. She recovered successfully and was discharged on a diet and 70 units of insulin daily, which did not adequately control her diabetes. Her diabetic state remained uncontrolled despite numerous attempts to improve it.

In March, 1941, she was admitted to the Massachusetts General Hospital where it was found that she had diabetes of the insulin-resistant type, as evaluated by insulin and glucose-insulin tolerance tests. The cholesterol was 159 mg per 100 cc.

\* We wish to thank Dr. Fuller Albright for allowing us to study this patient.



of plasma, calcium 10.8 mg per 100 cc of serum, phosphorus 2.9 mg per 100 cc of serum, phosphatase 2.1 Bodansky units. Roentgen-rays of the skull and spine demonstrated mild osteoporosis. The sella turcica was normal. A perirenal air insufflation was thought to show a suspicious shadow in the region of the right adrenal. The 17-ketosteroid assays were 25.6 and 24.3 mg per 24 hours. The patient was given a ketogenic diet, without insulin (although she had been taking 70 units previous to admission). She did not develop ketosis and noted no subjective change except increased weakness. When she was given a normal diet she felt better but there were no appreciable changes in her blood or urinary findings.

In June, 1941, she was admitted to the Massachusetts Memorial Hospitals complaining of headaches. Her blood pressure was 142 mm Hg systolic and 100 mm Hg diastolic. A lumbar puncture, performed to relieve the headaches, showed an initial pressure of 220 mm of water (although the patient possibly was not relaxed). An intravenous pyelogram was interpreted as showing an enlarged left kidney. The 17-ketosteroid excretion was 18 and 14.4 mg per 24 hours respectively, on two occasions. She was discharged on a diet of carbohydrate 150 grams, protein 70 grams, fat 60 grams, and was told to take 45 units of protamine insulin daily. A later course of roentgen-ray therapy directed to the pituitary had little apparent effect on her diabetes.

Physical examination revealed a middle-aged woman with plethoric features and marked girdle obesity (figure 7). The blood pressure was 140 mm Hg systolic and 90 mm Hg diastolic. Black hair was present in increased amounts on the upper lip, chin, arms, legs, and abdomen, the latter having a male pattern. The skin was thin, reddish-purple striae were present over the shoulders and hips, and the superficial veins were prominent. There were one or two (spontaneous) bruises on her lower extremities. The thyroid was palpable and there was a firm nodule to the right of the isthmus. The lungs and heart were normal. The abdomen presented a large panniculus of fat, no internal organs or masses were palpable. Pelvic examination revealed hypertrophy of the major and minor labiae, and a clitoris about twice the normal size. Neurological examination was normal.

Blood cell counts were normal. Repeated urinalyses showed a 4 plus sugar reaction. Fasting blood sugars varied from 180 to 252 mg per 100 cc. There were 95 m eq of chloride per liter of serum, total protein, 6.9 grams per 100 cc of serum. The glucose and insulin tolerance test gave the following values: 204, 222, 270, 292, and 345 mg of sugar per 100 cc of blood, the samples having been taken at 0, 30, 60, 90 and 120 minutes respectively. Two determinations of the basal metabolic rate were within the normal range. Roentgen-rays of the sella turcica and intravenous pyelograms were normal.

The patient was given a constant diet of protein 71, carbohydrate 162, fat 58, without insulin. On this regimen she excreted varying amounts of sugar in the urine, ranging from 42 to 66 grams per 24 hours. She did not show a negative nitrogen balance. After she had been maintained on the above diet for a control period of 16 days, she was given thiouracil 0.6 gram per day from September 1 to 12, 1 gram per day from September 13 to 21. She displayed mild ketonuria during the last week of treatment. Results of this therapy are discussed separately.

On September 8, 1942, she was discharged on her previous diet of carbohydrate 150, protein 70, fat 60, and was told to take 24 units of protamine insulin daily before breakfast. She has been taking thiouracil 0.2 gram daily for eight months but has noted no change in her hirsutism.

*Discussion* These three patients present certain of the manifestations of Cushing's and of the adrenogenital syndrome.

The first patient (M L) is a good example of the adrenogenital syndrome coming on after menarche. The excellent musculature, clitoral enlargement, masculinization and somewhat elevated 17-ketosteroid excretion are characteristic. The distribution of fat, and tendency toward insulin resistance are more commonly associated with Cushing's syndrome, however



FIG 7 (Case E M) Note the obesity of the trunk contrasted with slim extremities. Hair and veins are prominent over the breasts. Legs show spontaneous bruises. Beard is not prominent, since patient had just shaved.

The slightly negative nitrogen balance may be related to the concomitant presence of chronic infection.

The second case (L T) is probably an example of the same disease in an older woman. This patient differs, however, in that she had much more acne, a normal clitoris, a normal glucose and insulin tolerance test and low 17-ketosteroid excretion.

It is quite evident that some functional alteration in physiology has occurred in both these patients. Neither had any clinical evidence of a pit-

utary lesion In both the ovaries were ruled out as a cause of the patient's trouble Surgical exploration showed some hypertrophy of one adrenal in the first patient The ablated adrenal of the second patient was normal

These patients demonstrate the inadequate correlation between morphology and function Certainly the severity and progression of these patients' symptoms is eloquent evidence of malfunction Yet the histological evidence of adrenal hyperfunction was slight in one and absent in the other Even so, the positive morphological findings in one of these "idiopathic" cases suggest that, with the coming of improved histological techniques, many cases will be removed from this classification

The third patient apparently fulfills the criteria for a diagnosis of Cushing's syndrome Yet here again we could not localize the primary anatomical etiologic factor in her disease Recently another such patient has been reported,<sup>48</sup> again emphasizing the inadequacy of our diagnostic aids Together, these three cases also provide all the comment necessary on the ineffectuality of surgery, roentgen and medical therapy on the progress of the hirsutism

*Hirsutism Associated with Pituitary Disease—Acromegaly* Hirsutism is sometimes associated with acromegaly One such case was observed in our group Because this patient came to autopsy we include her clinical history and postmortem findings

*Case 4* M D, a 50-year old white unmarried female, was admitted to the Second Medical Service of the Boston City Hospital, on July 11, 1941, in marked cardiac failure Twenty years previous to her admission her features grew coarse, her hands enlarged, her voice deepened, and headaches began to accompany her menses Seventeen years before admission she underwent a leiomyomectomy, followed by amenorrhea, which persisted until two years previous to admission, when she had several normal catameniae Amenorrhea then recurred Sixteen years prior to the present entry, she developed diabetes mellitus and thyrotoxicosis An adenomatous colloid goiter was removed Six years later, hirsutism developed During the four years preceding admission, fasting blood sugars ranged from 178 to 322 mg per 100 c c and blood pressures from 210 mm Hg systolic and 110 mm Hg diastolic to 140 mm Hg systolic and 80 mm Hg diastolic

Physical examination revealed an orthopneic, well-nourished, middle-aged woman with acromegalic features The upper lip and jaw were very hairy The skin was thick and coarse The hands and feet were large The temperature was 98° F, pulse 100, respiratory rate 30 per minute, and blood pressure 148 mm Hg systolic and 112 mm Hg diastolic A thyroidectomy scar was present, and an increased amount of adenomatous thyroid tissue was palpated The lungs revealed dullness and moist râles at the left base posteriorly The heart was enlarged, and there was a systolic murmur at the apex The liver was enlarged and tender The pubic hair had a male pattern, but there was no hypertrophy of the clitoris There was extensive pitting edema of the ankles, legs, and sacrum The neurological examination was normal

Laboratory tests revealed the following Blood cell counts were normal Numerous urines showed 1 plus to 4 plus albumin, and no sugar The blood Hinton reaction was negative The non-protein nitrogen was 25 mg per 100 c c, chlorides 100 m eq per liter, cholesterol 250 mg per 100 c c, calcium 10 mg per 100 c c of

serum, phosphorus 39 mg per 100 cc of serum, phosphatase 45 Bodansky units, total protein 5 grams per 100 cc. Numerous fasting blood sugars were less than 120 mg per 100 cc, with one exception which was 175 mg per 100 cc. The roentgen-ray of the skull was interpreted as showing Paget's disease, roentgen-rays of the hands showed elongation of the first metacarpals. The basal metabolism was minus 12 per cent (after partial recovery from cardiac failure). The follicle stimulating hormone assay was positive for 18 rat units. The 17-ketosteroid excretion was 4 mg per 24 hours. A glucose-insulin tolerance test showed values of 107, 144, 179, 175, 222 mg per 100 cc, specimens having been taken at 0, 30, 60, 90, and 120 minute intervals.

The patient's cardiac failure improved. She was given desiccated thyroid (U S P) 06 gram per day and showed further improvement.

On September 23, 1941, the patient reentered the hospital, with a recurrence of her congestive failure. She failed to respond to therapy and died.

*Postmortem Examination* The external appearance was that already noted in the antemortem examination. The liver was slightly enlarged (2,480 gm) extending 4 cm below the costal margin. The spleen (320 gm) showed a small area of infarction. The pleural cavity had many adhesions on the right, with a small quantity of serous fluid in the right base. The heart (620 gm) showed hypertrophy of both ventricles and considerable dilatation of the right auricle. Both coronary arteries were atheromatous. An adherent, pale-gray thrombus was present over both surfaces of the anterior half of the interventricular septum.

The examination of the endocrine organs was as follows:

*Pituitary* The organ weighed 1 gram. The anterior lobe contained a soft necrotic area, which comprised one-third of its bulk. Histologically it was found that much of the anterior lobe consisted of a pituitary eosinophilic adenoma largely destroyed by a recent infarct. The cells of the remaining portion of the gland showed a predominance of basophiles.

*Thyroid* The lateral lobes were of usual size, and contained numerous cysts and much fibrous tissue. Microscopically there was great variation in the size of the follicles, most of which were filled with old colloid. There was no epithelial hyperplasia.

*Adrenals* The right adrenal weighed 16 gm, the left 12 gm. They were firm, and there was a very deep yellow color of the cortex. Histologically there was no hyperplasia of the cortices.

*Genital organs* The uterus was small and firm, displaying an inactive endometrium. The ovaries were small (5 cm in diameter). No follicles were seen.

The pancreas and parathyroids were not grossly or histologically remarkable.

*Discussion* This patient's clinical history suggests that 25 years previous to our observation, she began to develop her pituitary tumor. The headaches at this time were probably due to enlargement of the neoplasm. In response to increased growth hormone production, her features grew coarse, and her hands and feet enlarged. A few years later, presumably as a response to increased thyrotropic and pancreatropic stimulation she developed hyperthyroidism and diabetes mellitus. As evidence of probable adrenal stimulation are the hirsutism and amenorrhea. About two years before her final admission, some reverse of a previously progressive process seems to have occurred. This was not brought about by the infarct found at postmortem examination, however, since the latter was of more recent occurrence. She had the onset of myxedematous symptoms, concurrent im-

provement of her diabetes and occasional menses. Despite improvement in most of her findings the hirsutism did not disappear. It is also interesting that the case shows marked secondary adrenal hypertrophy which probably explains the persistence of facial hair. A similar case of acromegaly reported by Kennedy (quoted by Schwartz<sup>24</sup>) underwent a post-hypophysectomy remission of all symptoms save the hirsutism. The low 17-ketosteroid excretion in this patient was probably due to poor clinical status.

We have been impressed by the number of our "idiopathic" cases who presented suggestive acromegaloid features. Half the group gave a history of increased growth and strength over that of similarly aged companions in their early life. Although most of the women were not tall, many had broad faces, heavy brows, prognathous jaws, large hands and stubby fingers, all suggestive of acromegaly. Four of these patients had goiters and one had suffered from thyrotoxicosis in the past. Two gave a history of persistent lactation for a long period of time. One patient had hyperplasia of the gums similar to the "partial acromegaly" described by Zondek<sup>40</sup>. This may be merely a congenital characteristic, however, since it has occurred in other members of her family.

*Hirsutism Associated with Adrenal Disease—Pseudohermaphroditism*  
According to the most accepted concepts, the pseudohermaphrodite represents virilization due to adrenal hyperfunction. We have observed one such case which exhibited "hirsutism" as a precocious appearance of abundant axillary and pubic hair. The face was not involved (figure 8).

*Case 5* B M,\* an eight year old white girl, was admitted to the Massachusetts Memorial Hospitals September 21, 1943. Her birth history was normal. At the age of one year, a doctor had noted unusual clitoral enlargement and had advised investigation. The family noted progressive enlargement of the organ but deferred treatment. The patient had always exhibited thoroughly feminine habits and was unaware of her abnormality. The family history was irrelevant.

The physical examination revealed a shy, feminine-acting girl, with a very deep masculine voice. She was slender and her body habitus was masculine. She was the size of a 12 year old girl, weighing 91 pounds and measuring 57 inches in height. Her strength was distinctly better than normal. The blood pressure was 150 mm Hg systolic and 70 mm Hg diastolic. She had considerable facial acne. The skin was seborrheic. The pubic and axillary hair was well developed. The thyroid was not enlarged. The heart and lungs were normal. No abdominal masses could be palpated. Pelvic examination revealed well developed labiae majorae covered with abundant hair. The clitoris was a large, penis-like structure, three inches in length, with a well-developed glans (figure 9). On the inferior surface a frenulum was present, running back into the vestibule. On the inferior aspect of the frenulum were several openings, one of which proved to be the urinary meatus. Cystoscopic examination revealed a normal bladder. The vagina was well-developed.

Laboratory studies revealed the following. Red, white, and differential blood cell counts and urinalyses were normal. The basal metabolic rate was plus 2 per cent. The fasting blood sugar was 94 mg per 100 c c, total protein 7.0 grams per 100 c c of plasma, calcium 10.9 mg per 100 c c of serum, phosphorus 3.8 mg per 100 c c of

\* We wish to thank Dr. Samuel Vose for allowing us to study this patient.

serum, alkaline phosphatase 114 Bodansky units, sodium 336 mg per 100 c c of serum. The glucose tolerance test gave the following values 125, 89, 100, and 60 mg per 100 c c, the samples having been taken at 0, 30, 60 and 120 minutes. The insulin tolerance test gave values of 111, 80, 85 and 90 mg per 100 c c, the samples having been taken as above. Intravenous pyelograms were normal. The sella turcica was

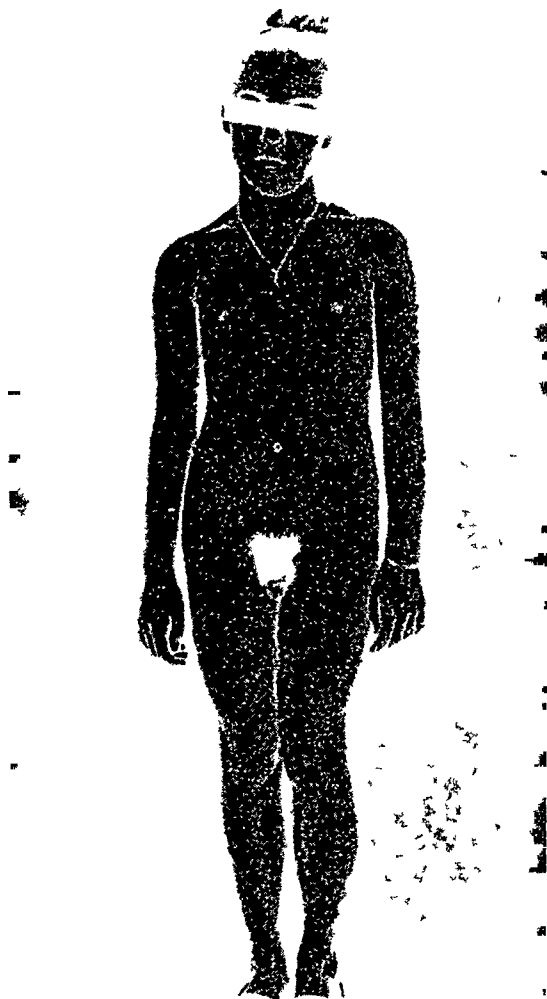


FIG 8 (Case B McI) Age 8 years. Note the boyish figure and good musculature.

normal. Roentgen-rays of the long bones and epiphyses showed development consistent with that of a 14 year old girl. There were 84 and 141 mg of 17-ketosteroids excreted per 24 hours in two samples assayed.

On October 8, 1943, an exploratory laparotomy was performed. The uterus, tubes, and ovaries were normal. Both adrenals were palpated, and the right was thought to be enlarged. On November 26, 1943, through a right lumbar incision, the right adrenal gland was found to be "larger than an adult's adrenal gland." A resection of one-half of the gland was performed, since the size of the other gland was

unknown Histological examination of the resected adrenal revealed cortical hyperplasia

Six months following the operation the patient's voice was of higher pitch although still resembling that of a boy Acne was much improved There was some increased areolar pigment and beginning mammary development The genitals were unchanged The laboratory studies were essentially unchanged The 17-ketosteroid excretion, however, had dropped to 3.8 and 4.4 mg per 24 hours, in two samples analyzed



FIG 9 External genitals of Case B McI The clitoris was about 3 to 4 inches long The urethra was one of the multiple openings in the frenulum Vagina about normal size

*Comment* This patient is a classical example of pseudohermaphroditism, presumably resulting from adrenal cortical hyperplasia Actually, it is the adrenogenital syndrome, beginning in embryonic life The body cells are in the process of differentiation and the effects of increased androgen production are marked The causative etiological lesion may be an adrenal tumor, adrenal hyperplasia, or a hyperfunction of some androgenic adrenal component (such as the X-zone)<sup>50</sup>

The effects of operation on the appearance of this girl are marked There has been a definite diminution in androgenic influences as demonstrated

by the beginning breast development, increase in vocal pitch, and lessened acne. The drop in the 17-ketosteroid excretion is a good chemical indication that there has been a diminution of the androgenic function of the adrenal. The genital malformation will undoubtedly require plastic surgery.

*Transient Hirsutism, Associated with Pregnancy*

A C,\* aged 28, a white primagravida, was admitted to the Boston Lying-In Out-Patient Department on September 19, 1941. The patient stated that her last menstrual period had occurred on July 23, 1941. In September, 1941, she first noted the appearance of rapidly growing blackish hair on her malar eminences, ear lobes, eyebrows and upper lip. By October, 1941, her chin, mammary areolae, arms and legs were involved. She had always had a male pubic hair distribution, but this had increased. The patient was not at all perturbed over her hirsutism, since her mother also had been hirsute during pregnancy, and had lost all the abnormal hair post partum.

Past history revealed that she had always been a "big girl." At 11 years she had weighed 125 pounds. Her catamenia began at 11 years, had occurred every 28 days, for a five-day period. Her first menses were associated with nausea, vomiting and dysmenorrhea.

Physical examination revealed an obese young woman with marked hirsutism. The temperature was 98.6° F, pulse 90, respiratory rate 20 per minute, weight 179 pounds and height 67 inches. The blood pressure was 125 mm Hg systolic and 75 mm Hg diastolic. Coarse black hair covered her upper lip, cheeks, chin and jaw, and grew out of her ears and ear lobes. There was increased hair on the legs and forearms, and a pronounced male pubic hair growth was present. The areolae of the nipples were surrounded by ten or twelve long dark hairs. The thyroid was diffusely enlarged. The clitoris was slightly hypertrophied. Pelvic findings were consistent with pregnancy of three months' duration. Otherwise, the physical examination was normal.

Roentgen-rays of the sella turcica were normal. The basal metabolic rate was minus 10 per cent. The 17-ketosteroid excretion was successively 15.04 and 13.92 mg per 24 hours (December, 1941).

The hirsutism continued to increase until February, 1942. Spontaneous depilation then occurred beginning about the ears and right side of the face. Later the hair on the abdomen and large patches on the thighs were denuded. The clitoris remained enlarged. In February, 1942, the patient had some vaginal bleeding which stopped spontaneously.

The patient went into a 20-hour labor on May 13, 1942. She had some uterine inertia and was delivered with low forceps. The child was given early formula feedings because of oligogalactia. The hirsutism was still present at delivery but disappeared entirely post partum.

*Comment* It is known that the adrenal enlarges in animals during pregnancy.<sup>11</sup> The hirsutism seen in human females during gestation is due presumably to similar adrenal hyperfunction. The fact that relatively few patients suffer from transient hirsutism of pregnancy suggests that other factors are also implicated. This patient had a familial history of hirsutism which suggests that genetic factors are involved. This case has several other points of interest. Although she was not hirsute previous to her

\*We wish to thank Dr. David Hurwitz for furnishing the information regarding this patient.



pregnancy, her "bigness," obesity, and male hair distribution are reminiscent of our "idiopathic" hirsute group. Whether the clitoris was enlarged before her pregnancy or as a result of it cannot be stated. The threatened abortion, uterine inertia, and oligogalactia also seem to indicate some lowering of typical feminine function, possibly due to androgenic influences. The beginning depilation before the delivery of this patient is difficult to explain. However, it has been shown<sup>51</sup> that estrogen excretion increases about the sixth month of pregnancy. It was at this time that the patient began to lose her hirsutism. With the increase in estrogens we might postulate that the estrogenic-androgenic ratio reached a better balance and the hirsutism diminished as a result.

Another patient with transient facial hirsutism of pregnancy whom we have seen did not lose her abnormal hair until after delivery. This individual was slender and had no family history of hirsutes. The 17-ketosteroid excretion ranged from 1.6 to 3.2 mg per 24 hours on three occasions. The values are actually lower than normal.

*Therapy.* The treatment of hirsutism is grossly unsatisfactory. Most patients attempt a purely local remedy by shaving, tweezing, depilation and electrolysis, all of which are temporary and annoying. As has been pointed out in a recent editorial, the more severe the cause of hirsutism the more likely the cure.<sup>52</sup>

There is general agreement that when the cause is a tumor, surgical removal is indicated. The results are often brilliant, with a complete reestablishment of all feminine functions and characteristics. However, even here the hirsutism may persist.<sup>53</sup> Also, in the case of adrenal tumors, the opposite gland may be secondarily atrophied and unable to maintain life function.<sup>31</sup> When the cause is a basophilic tumor of the pituitary, either surgical or roentgenological treatment is generally unsatisfactory. In the case of adrenal hypertrophy, resection of the cortex and unilateral adrenalectomy have caused only slight transient improvement in most cases. This certainly was our experience in two cases (M. L. and L. T.).

Androgens and estrogens are produced by both males and females. Although it is often difficult or impossible actually to demonstrate increased androgen production in hirsutism, it is frequently assumed that imbalance in the androgen-estrogen ratio exists. It would seem that hormonal therapy might thus cause disappearance of masculinization.

Synthetic and natural estrogens have been tried, although results have not been encouraging. We have given synthetic estrogens (diethylstilbestrol) to the two post-menopausal cases in 1 to 2 mg daily doses for eight months without effect on the hirsutism. In six other cases (R. M., M. L., M. F., F. M., K. C., S. D.) both synthetic and natural estrogens given in adequate doses for similar periods of time had no effect on the hirsutism. One patient (R. M.) had definite increase in her acne during therapy with stilbestrol. It is of passing interest to note that estrogens cause adrenal hyper-

trophy in animals and presumably have the same effect in man, as suggested by the growth of pubic and axillary hair in hypo-ovarian dwarfs under estrin therapy<sup>9</sup> Thus it would seem that estrogens might possibly enhance the condition already present

Progesterone, in large doses, is reported to cause adrenal atrophy<sup>45, 46</sup> This is apparently mediated through the inhibition of luteinizing hormone of the pituitary, which is thought to stimulate the adrenal cortex<sup>47</sup> One attempt to diminish adrenal function by this means (M L) was an apparent failure In three patients, we successfully reestablished normal catamenia by the concomitant use of estrogens and progesterone Even after menstruation occurs in a normal fashion for several months, the hirsutism persists Simple reduction of weight has had no effect on the hirsutism In four patients the effect of the new antithyroid drug 2-thiouracil, introduced by Astwood,<sup>54</sup> has been noted In the course of study it was noted that large amounts of thiouracil were taken up by the adrenals of both animals and man<sup>55</sup> We also observed that an occasional hyperthyroid patient treated with this drug exhibited chloride retention, depression of CO<sub>2</sub> combining power and slight edema<sup>56, 57</sup> Since these patients had no evidence of renal or cardiac disease, and had normal serum proteins, we thought that this effect was possibly mediated through the adrenals

Each of the patients was first brought into the hospital and a balance study performed, to determine the effects of thiouracil administration on nitrogen and electrolyte balance Slight retention of nitrogen, sodium, chloride, creatine and creatinine was noted A full report of these results is to be found elsewhere<sup>57</sup> The glucose and insulin tolerance tests and 17-ketosteroid excretion were not affected The four patients have been maintained on thiouracil\* in doses of 0.2 to 0.4 gram daily for 10 months Two of the patients who have diabetes mellitus have discontinued insulin and have remained without sugar in the urine while on therapy This is probably not a direct result of drug therapy but due to the fact that they have lost some weight and have been following their diet more strictly

One woman (G K) whose hair was quite gray now has a definite admixture of yellow She has seen no change in the character or growth of her facial hair, although it is now removed with greater ease After eight months of therapy (0.4 gram daily) the drug was discontinued in this patient, due to the onset of symptoms of myxedema and depression in her basal metabolic rate

Two other patients (L M and K McG) state that they do not shave as frequently as before the treatment, although we can note little change The fourth woman (E M) has observed no effect of thiouracil on her diabetes or facial hirsutism The abnormal distribution of body hair has not been affected

\* We wish to thank the Lederle Company, Pearl River, New York, for the thiouracil (Deracil) used

## DISCUSSION

A purely clinical differentiation of hirsutism is often difficult because it occurs in so many different conditions. It is important to note that the length of time since the onset of symptoms is often of great value in excluding a malignant process. Although the severity of masculinization is often suggested to differentiate the "idiopathic" variety from pituitary, adrenal and ovarian types of hirsutism, our series would not bear out this fact. Likewise, patterns of fat distribution, the quality and location of the abnormal hair produced, and the presence or absence of clitoral hypertrophy, although formerly considered to be of great significance, are of little practical use in differentiating among the various lesions.

Pituitary lesions have as their most valuable diagnostic aids the finding of an enlarged sella turcica by roentgen-ray, or a defect on the visual field by perimetry. Symptoms relative to increased intracranial pressure, or cerebral irritation may occasionally be helpful. The physical and metabolic changes once thought typical of pituitary basophilism may occur with adrenal cortical lesions.

In diagnosing adrenal lesions, the palpation of an abdominal mass is most helpful. Careful studies of the kidney-adrenal area with pyelograms, and possibly perirenal air injections, may yield valuable confirmatory information.<sup>58</sup> Great increases in 17-ketosteroid excretion, especially of the beta and non-alcoholic fractions, are valuable in diagnosing cases of adrenal carcinomata.<sup>42, 43</sup> Lesser increases in total 17-ketosteroid output occur in some instances of "hyperplasia."

Arrhenoblastomata of the ovary are not usually associated with hypertension, disordered carbohydrate metabolism, osteoporosis or polycythemia. It has been stated that the presence of a pelvic mass, when associated with hirsutism, an enlarged clitoris and normal excretion of 17-ketosteroids, should make one suspicious of an ovarian tumor.<sup>48</sup> We have seen one patient (S W) who had severe virilization, an enlarged clitoris, low 17-ketosteroid assays and a pelvic mass, whose ovarian "tumor" proved to be a tubo-ovarian abscess at operation. Similar findings may also occur with diffuse luteinization of the ovaries.<sup>28</sup> If, after careful search, ovarian, pituitary or adrenal causes are ruled out, the case then becomes one of "idiopathic" hirsutism.

The relationship between heterosexual hypertrichosis and certain instances of adrenal hyperfunction has been quite well established. This is most clearly acceptable with the demonstration of an adrenal lesion per se. In the case of pituitary tumors associated with hirsutism, adrenal hypertrophy is often demonstrable, and the mechanism seems adequately explained by an excessive stimulation of the adrenal cortex by pituitary adrenotropins. Ovarian tumors associated with masculinization presumably produce substances similar in action to the cortical steroids. There are also rare masculinizing ovarian tumors actually composed of functioning adrenal cortical

cells<sup>10</sup> When none of these explanations obtains the case becomes "idiopathic" This is always an unsatisfactory diagnosis and especially so when we realize that most hairy women fall into this classification At present the cause of this condition is generally thought to reside in an inherent, constitutional defect in the hair follicles themselves, influenced perhaps by racial or familial genetic factors Although the hereditary tendency toward hairiness is probably present in many individuals, we believe that the clinical similarity of many of these idiopathic cases, to those associated with either primary or secondary hyperfunction of the adrenal cortex, is suggestive Although 17-ketosteroid determinations are often normal or even subnormal, some cases of "idiopathic" hirsutism have been found associated with increased titers<sup>59</sup> of androgens, or to have increases in the excretion of androgens in relation to estrogens<sup>60</sup> This seems further to suggest adrenal cortical hyperfunction At present the pathologist can give little help in the situation because of current lack of methods adequate to demonstrate altered function in cells which may look anatomically normal under the usual stains

We feel that with the development of better histochemical technics, more generally applicable methods of specific steroid assay and more sensitive tests of adrenal cortical function than now exist, many cases of "idiopathic" hirsutism will be reassigned to a more proper category Also, we feel that further knowledge of the enzyme systems involved in adrenal physiology may point the way toward a more rational therapeutic attack on hirsutism

### SUMMARY

Normal human hair production is apparently the result of (a) inherent qualities within each hair follicle, and (b) endocrine influences The effects of hormonal control on hair growth are especially apparent in diseases affecting the adrenals, anterior pituitary, thyroid, and gonads Hirsutism in females is often associated with anterior pituitary, adrenal cortical and ovarian disease, especially of a neoplastic character The majority of hirsute women, however, demonstrate no gross endocrine abnormality and are classed as examples of "idiopathic" hirsutism

Twenty-nine cases of "idiopathic" hirsutism have been studied in some detail Twenty-four of the cases had heavy beards requiring daily shaving, 23 had the male type of pubic hair distribution Clitoral enlargement was present in 11 cases Thirteen had menstrual abnormalities Obesity was present in the majority Glucose-insulin tolerance tests were abnormal in 19 cases, suggesting the possibility of an insulin resistant type of carbohydrate defect The 17-ketosteroid excretion was normal or subnormal in the majority of the group Case histories of three patients, including a metabolic balance study of one, are given

One case of hirsutism associated with acromegaly has been reviewed, with autopsy findings

One case of pseudohermaphroditism is recorded in detail

Two cases of transient hirsutism of pregnancy were studied. One case is reported in detail.

The therapy of hirsutism is generally unsatisfactory. In our series, both hormonal and operative measures were employed without success. Four cases were treated with thiouracil in doses from 0.2 to 0.4 gram daily for eight months. The results were not encouraging.

The differential diagnosis of hirsutism is briefly discussed. It is felt that with increased knowledge of histochemical technics, steroid chemistry and enzymology, many cases of "idiopathic" hirsutism will be found to have evidence of hyperadrenocorticism.

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# PENICILLIN TREATMENT OF SULFA-RESISTANT GONORRHEA, RESULTS OF 500 CASES TREATED WITH 50,000 UNITS OF PENICILLIN \*

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DURING the early observation of the effects of penicillin on various organisms the gonococcus was found to be susceptible, and during 1943 its successful use in several small series of cases was reported<sup>1, 2, 3</sup> Recently Ferguson and Buckholtz,<sup>4</sup> in reporting the results of treatment in 735 cases of sulfonamide resistant gonorrhea with varying doses of penicillin, indicated that a dosage of at least 100,000 Oxford units was necessary for uniformly satisfactory results. During the summer of 1943 O'Reilly General Hospital, among a number of other general hospitals, was assigned the task of treating several groups of sulfa-resistant gonorrhea with varying doses of penicillin. Following this experimental period, the Office of The Surgeon General, in September 1943, advised that the dosage be established at 50,000 Oxford units as an initial course, with 100,000 Oxford units to be used subsequently in the event of failure to obtain adequate response to the initial therapy. When a case failed to respond to the second course of penicillin, the treatment was to be considered a failure and other means of therapy were to be initiated. The results of such treatment in 500 consecutive cases of sulfa-resistant gonorrhea form the basis of this report.

Approximately 90 per cent of these cases were received as transfers from various station Hospitals of the Service Command where they had failed to respond to the administration of sulfonamides. The remainder were received as casualties or admitted from the local command, and had ineffectually received sulfonamide therapy under our care. In all cases treated with penicillin the urethral discharge had persisted and cultures were positive for *N gonococcus* at least three days following the discontinuance of two courses of sulfonamide, each course consisting of at least 20 grams of sulfathiazole or sulfadiazine over a five-day period.

## ADMINISTRATION OF THE DRUG

Penicillin powder was dissolved in sufficient sterile, distilled water so that 2 c c contained 10,000 Oxford units and was routinely administered intramuscularly. Care was maintained to group the cases so that freshly prepared solutions were always used. The original course of 50,000 Oxford units was given in doses of 10,000 Oxford units every three hours for five doses.

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Where it was necessary to administer 100,000 Oxford units, injections of 10,000 Oxford units were given at hourly intervals for 10 doses. During the first few weeks of our program the patients were required to remain in bed five days following penicillin therapy. Later the patients remained in bed only on the day they received penicillin and this was done chiefly for the purpose of convenience in administration. No other specific measures were carried out and the patients partook of food and fluids as desired. There were no serious reactions to the drug. Most of the patients admitted to having slight burning sensations deep in the muscles for no longer than a few hours but this was never severe and in no cases was it necessary to use other than the gluteal regions for injections. A temperature of 99° to 100° F on the day of injection was common. One patient experienced an elevation to 104° F, but this was probably due to a flare-up of an accompanying acute balanitis. Generalized urticaria followed the injection of penicillin in five instances. The longest duration of the urticaria was five days. Several days following the disappearance of the urticaria each of these cases was given 0.1 c.c. of dilute penicillin solution intradermally and in no instance was there any skin reaction observed. In none of these cases was a second dose of the drug necessary so that the effect of a repeated intramuscular injection was not observed.

#### CRITERIA FOR CURE

During the early experimental use of penicillin our cases were followed over a period of 21 days subsequent to therapy. Material obtained by prostatic massage and centrifuged urine sediment at 48 hours, 7 days, 14 days, and 21 days was cultured by the Laboratory Service on chocolate blood agar plates containing proteose No. 3 peptone and yeast extract and was cultured for 48 hours at 37° F in a 10 per cent CO<sub>2</sub> atmosphere. No case was pronounced cured if any of these cultures were reported to be positive for *N. gonococcus*. It was found that in most instances when the cultures taken at 48 hours and at seven days following therapy were negative the subsequent cultures were also negative, but in a few instances a positive culture was found for the first time after therapy on the fourteenth or twenty-first day.

Later in the course of this study all cases were observed over a period of seven days, or longer if clinically indicated, before discharge to duty or institution of further therapy. In all cases in which material could be obtained by stripping the urethra, cultures were obtained 48 hours and seven days following therapy. If no material could be obtained from the urethra or if cultures or smears on available serous discharge were negative at the end of seven days, the case was considered to be cured of gonorrhea.

In all cases returned to duty from the local command an inspection for urethral discharge was required at weekly intervals until three weeks had elapsed following therapy. As previously noted, over 90 per cent of all

cases were received from other commands and were returned to their organization on discharge from this hospital. In such cases the soldier was instructed to report to his medical officer and a form letter requesting examination of the soldier at weekly intervals for three weeks was forwarded to his organization commander. This letter was to be returned to us with a statement by the organization surgeon as to the results of his examination. Responses to this follow-up letter were received in only about 50 per cent of the cases. Admittedly, it is more than possible that some cases which relapsed following discharge from this hospital were never reported to us or returned to us for treatment. However, after due consideration, we feel that the number of such cases which were not reported would be small and would not affect our statistics to any great extent. Actually, only six cases were returned to us for treatment after what was considered a relapse of symptoms.

### RESULTS

Almost without exception, in those who responded to therapy, there was a remarkable decrease in the symptoms of burning and frequency and in the amount of urethral discharge within a period of six hours following the first injection of penicillin. By the next day the urethral discharge was usually scanty and serous in character. At the end of 48 hours the discharge had almost ceased and 456 cases had negative cultures at that time. However, 18 of these cases subsequently showed a positive smear or culture for *N gonococcus* and only 438, or 87.6 per cent, were finally considered cured by one course of 50,000 Oxford units.

The 62 cases that did not respond favorably to the first course of 50,000 Oxford units of penicillin were given a second course of 100,000 Oxford units. Following this dose 45 cases became culturally negative for *N gonococcus* and symptom free. However, a urethral discharge and positive culture persisted in 17 cases. After additional injections of penicillin to a total of 350,000 Oxford units and local therapy all cases became culturally negative for *N gonococcus* and three became asymptomatic. Fourteen cases continued to have a urethral discharge due to secondary infection.

An attempt was made to determine whether the cases which failed to respond to penicillin harbored a penicillin-resistant strain of *N gonococcus*. The organisms found in 30 unselected cases were tested for penicillin sensitivity as compared to a standard Oxford strain of *Staphylococcus aureus* whose growth was inhibited by 0.5–0.3 Oxford units of penicillin and considered "sensitive." In the *N gonococcus* organisms tested for sensitivity, all were inhibited in a range of from 0.5 to 0.05 unit and were considered "sensitive" to "very sensitive." Of these 30 cases tested, six failed to respond to the injection of 50,000 Oxford units and two cases were failures after an additional 100,000 Oxford units. No relationship to the penicillin sensitivity of the organisms involved in these cases could be demonstrated.

## COMPLICATIONS OF GONORRHEA

Gonorrheal arthritis was the most debilitating and serious complication encountered and was seen in eight cases. As far as could be determined, the course of this complication was not as favorably influenced by penicillin as other similar cases treated with sulfonamides have been. In all eight cases of gonorrheal arthritis, the accompanying urethritis was apparently cured. Acute epididymitis was seen in 15 cases. It was not thought that the course of this complication was shortened by penicillin and usually required 14 to 21 days before subsidence of symptoms.

Cases of long standing gonorrheal urethritis presented the most difficult problem in this series of cases. Seventeen of our cases fell into this group, all having had intermittent or persistent urethral discharge for a period of from one to 15 years, complicated by the presence of urethral stricture, periurethral abscess, obstruction of Littre's glands, or chronic prostatitis. None of these 17 cases responded to treatment with penicillin alone and it was only after additional prolonged local therapy that they became culturally negative for *N gonococcus*. Fourteen of these cases, although negative for *N gonococcus*, continued to have a persistent chronic urethritis which was resistant to all types of therapy.

## SUMMARY AND CONCLUSIONS

1 Of 500 consecutive sulfa-resistant cases of gonorrhea treated intramuscularly with 50,000 Oxford units of penicillin, 438 or 87.6 per cent became asymptomatic, culturally negative and were presumably cured.

2 Of the 62 cases of therapeutic failures after the initial course of penicillin, 45 were apparently cured after an additional course of 100,000 Oxford units, making a total of 96.6 per cent satisfactory results.

3 Seventeen cases of long standing chronic urethritis, originally on a gonorrheal basis but complicated by mixed infection, failed to respond satisfactorily to penicillin alone.

4 Penicillin did not have any specific effect on such complications of gonorrhea as acute epididymitis and arthritis in the few cases observed.

5 Except for the development of mild urticaria in five cases, there were no complications following injection of penicillin.

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# THE CLINICAL INTERPRETATION OF INSULIN INDUCED KETONURIA<sup>1</sup>

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TRANSIENT ketonuria in association with aglycosuria observed in insulin treated diabetics presents an apparent paradox. Such an observation was not uncommon at the time protamine zinc insulin was becoming popular. As pointed out by Mirsky<sup>1</sup> the older theories concerning ketogenesis are still invoked whenever a clinical problem involving ketonuria is found. The standard texts on diabetes mellitus dwell lightly upon the newer concepts concerning ketogenesis. The significance of insulin induced ketonuria, therefore, is frequently misunderstood and the condition is treated by additional insulin.

In 1935 Somogyi<sup>2</sup> observed the "causal connection between hypoglycemia and ketosis". Since this time he has expanded his studies of this phenomenon<sup>3,4</sup>. His work forms important supporting evidence for current concepts of ketogenesis. The clinical importance of these concepts will be demonstrated in this paper by a variety of cases in which we have observed acetonuria in association with hypoglycemia induced by insulin. In none of the cases were blood ketones determined so that the only evidence of increased blood ketone level was the finding of acetone in the urine. These cases illustrate the failure on the part of clinicians in general to appreciate the causes and clinical implications of this phenomenon. In reporting these cases the necessity for clinical alertness in recognizing this apparent paradox is emphasized.

## CASE REPORTS

*Case 1* A 40 year old male, whose past health had always been excellent, entered the hospital at 6 30 p m. The family history was negative. For several days prior to admission he had noted increasing weakness, polyuria and polydipsia. He also complained of blurred vision and increasing drowsiness. Physical examination revealed an ambulatory, drowsy male. His sensorium was dulled but did not interfere with his cooperation. The pulse was 62, blood pressure 114 mm Hg systolic and 74 mm diastolic, respirations 28 per minute, and the oral temperature was 97.6° F. There was a marked acetone odor to the breath. The physical findings, in general, were normal. A number of sebaceous cysts were present.

On admission his blood sugar was 500 mg per cent and a urinalysis revealed 4 plus sugar, 4 plus acetone and 4 plus diacetic acid. Facilities for determining CO<sub>2</sub> combining power were not available at that time. The diagnosis of diabetes mellitus was made and insulin therapy instituted. Seventy-five units of regular insulin were given in divided doses during the first four hours (table 1). Five hours after institution of treatment diacetic acid was no longer present, acetone was 3 plus, and sugar was 3 plus. Twenty units of regular insulin were given a half hour later and one hour after this an additional 10 units were injected. This was given although the

<sup>1</sup> Received for publication October 7, 1944

response to treatment, which might have been suspected five hours after treatment began, was now definite in that the urine sugar and acetone had both decreased to 1 plus. Eight hours after treatment began 10 more units of regular insulin were given although only traces of sugar and acetone were present in the urine. The urine specimen, obtained before breakfast, revealed no sugar but a trace of acetone. A blood sugar taken before breakfast and before 20 units of regular insulin were given was 47 mg per cent. The urine sugar remained negative one hour after breakfast,

TABLE I

Case F J B Age 40 W— Ht 70 Wt 150		Urine			Diet C 200, P 90, F 80		
Date	Time	Sugar*	Acetone	Diacetic Acid	Blood Sugar** Mg %	Insulin	Misc
4/18/44	6 30 p m	4+	4+	4+	(Admission) 500	RI U-40	
	7 20 p m	4+	4+	3+			
	8 20 p m	4+	4+	3+			
	9 00 p m					RI U-15	1 glass milk and 1 slice dry toast
	9 20 p m	4+	4+	3+			
	10 20 p m	4+	4+	1+		RI U-20	
	11 20 p m	3+	3+	Neg			
	Midnight					RI U-20	
4/19/44	1 0 a m	1+	1+	Neg		RI U-10	
	4 00 a m	tr	tr	Neg		RI U-10	Insulin given with breakfast
	7 00 a m	Neg	tr	Neg	47'	RI U-20	
	8 00 a m	Neg	tr	Neg			1 glass orange juice and 1 slice dry toast
	10 00 a m	tr	3+'	Neg			
	11 00 a m	2+	1+	Neg			
	Noon					RI U-20	Insulin given with lunch
	1 00 p m	2+	0	Neg			

\* Benedict Qualitative Technic

\*\* Venous Blood—Folin Wu Technic

but showed a trace two hours after this. However, the acetone showed an inordinate rise to 3 plus over the same time interval. Additional carbohydrates in the form of orange juice and toast were given and, in response to this, one hour later the urine sugar increased to 2 plus but the acetone diminished to 1 plus. Following the noon meal, the acetone disappeared or was present only in traces despite a persistent glycosuria which ranged between 2 and 4 plus throughout the rest of the day.

The patient came under my observation on the third day of his illness and was regulated ultimately on a diet of 250 grams of carbohydrate, 100 grams of protein, and 100 grams of fat. Protamine zinc insulin U-15 was administered 45 minutes

before breakfast daily. On this regimen, the patient was usually aglycosuric and always ketone free. Nocturnal hypoglycemia did not occur as the blood sugar at 3 a m was 98 mg per cent and the fasting blood sugar at 6 15 a m was 82 mg per cent. The patient was discharged following an uneventful convalescence from surgical excisions of all sebaceous cysts.

Table 1 illustrates the pertinent features of this case during the ketotic stages of the first 24 hours. The initial ketonuria was caused by excessive glycogenolysis which was extreme because the patient was approaching diabetic coma. This initial ketonuria, therefore, is diabetic in origin. The response to the first 75 units of insulin was quite satisfactory but at this point a proper evaluation of the urinary findings would have led to more conservative use of insulin and the judicious addition of carbohydrate feedings at intervals. The excessive use of insulin which followed produced a hypoglycemic state which was proved by the 47 mg per cent blood sugar level obtained before breakfast (7 a m). This was followed by a continued absence of sugar in the urine and a sudden increase in acetoneuria. Thus, we note that there has been a secondary *increase* in acetone as the glycosuria *diminished* and this was followed by the disappearance of the acetone, although the glycosuria *increased* and remained elevated. This secondary increase in acetone is *not* a reflection of disturbed carbohydrate metabolism secondary to a diabetic crisis, but as the case illustrates, is the response to an *insulin induced hypoglycemic state*. A realization of this mechanism would have obviated the hypoglycemia and the resultant rise in ketonuria. The case demonstrated that the ketogenic action of insulin when used in excessive amounts interferes with the prompt and proper regulation of the diabetic patient and produces a misleading ketonuria.

*Case 2* A 39 year old married female was seen for the purpose of changing her diabetic regimen from regular insulin to protamine zinc insulin. The patient was a known diabetic of eight years' standing. The disorder was discovered while the patient was recuperating from an appendectomy. Her family history was negative and the patient's past health had been excellent. The diabetes had always been asymptomatic. For two years she had been taking 10 units of regular insulin 20 minutes before each of three equicaloric meals. The diet was approximately 150 grams of carbohydrate, 70 grams of protein, and 100 grams of fat. For one month prior to observation her diet consisted of 210 grams of carbohydrate, 80 grams of protein, and 60 grams of fat supplemented by concentrated vitamins A and D. Several sets of 24-hour urines preserved with toluene were collected over two day periods and showed that the daily glycosuria ranged between 0 and 14 grams. The admission physical examination, routine blood counts and urinalyses were normal. During hospitalization the patient continued the same diet. Protamine insulin U-35 was given 45 minutes before breakfast. Urine specimens were collected from meal to meal and were examined quantitatively by the Somogyi technic<sup>5</sup>. The fourth night following daily injections of the 35 units of protamine zinc insulin a hypoglycemic state occurred (blood sugar at 3 a m 49 mg per cent) and this was followed by the appearance of acetone in the urine (table 2, heavy bordered section). The insulin was reduced to 20 units and additional carbohydrates were given at bedtime. Nocturnal hypoglycemia was not present subsequently and the urines were always free of acetone. Fasting blood sugar on the two mornings prior to discharge on the eleventh day was 113 and 126 mg per cent respectively. The glycosuria for each 24 hour period ranged between 21 and 15 grams with total available carbohydrate in the diet approximating 260 grams. The patient was instructed to continue on this regimen. No follow-up observations have been made but she was reported as remaining well.

In contrast to Case 1, this case shows that an appreciation of the ketogenic potentialities of insulin leads to a prompt reduction in the insulin. In this case, such a reduction was followed by permanent disappearance of ketonuria without sacrificing

the diabetic regulation. In fact, diabetic regulation was *improved* following the use of *less* insulin as judged by fasting blood sugars within the range of normal and a perceptible decrease in the total amounts of glycosuria for each succeeding 24 hour period (table 2). This case is typical of many cases observed by Somogyi<sup>2</sup> and by us

TABLL II

Case F C W— Age 39 Ht 61 Wt 122	Fractional Urine Examinations								Diet C 210, P 80, F 60		
	Breakfast to Lunch		Lunch to Supper		Supper to Midnight		Midnight to Breakfast				
Date 1943 September	G*	A**	G	A	G	A	G	A	Total Glycosuria Gm	Blood Sugar*** Mg %	Insulin Etc
17 to 18	12	0	14	0	6	0	0	0	32		6 15 a m 9/17/43 PZI U-35
18 to 19	23	0	18	0	4	0	0	0	45		No change
19 to 20	27	0	21	0	4	0	0	0	52		No change
20 to 21	16	0	14	0	7	0	0	+	37	3 00 a m 9/21/43 49	No change
21 to 22	18	tr	13	0	3	0	0	+	34	3 00 a m 9/22/43 62	6 15 a m 9/21/43 PZI U-25
22 to 23	16	tr	12	0	5	0	0	tr	33		6 15 a m 9/22/43 PZI U-20
23 to 24	19	0	5	0	3	0	0	0	27	3 00 a m 9/24/43 81	1 Orange h s No change in PZI
24 to 25	18	0	3	0	tr	0	0	0	21		No change
25 to 26	13	0	2	0	0	0	0	0	15	6 00 a m 9/26/43 113	No change
26 to 27	17	0	4	0	0	0	0	0	21	6 00 a m 9/27/43 126	No change

\* Glucose Expressed as Grams—Somogyi Technic<sup>5</sup>

\*\* Acetone Test (Denco)

\*\*\* Capillary Blood Analysis—Folin Micromethod

**Case 3** A 24 year old male first came under my observation during June 1943. His glycosuria had first been noted during July 1942 while he was hospitalized elsewhere because of an acute respiratory infection. The records of this hospitalization and subsequent out-patient care were made available to us. The patient's past history was irrelevant and his family history was entirely negative. Glycosuria was found on admission and on repeated examination. The patient admitted on direct questioning that polyuria, polydipsia, and polyphagia had been present for some time. The respiratory infection subsided promptly and the diagnosis of diabetes mellitus was made. The patient was placed on an unmeasured restricted carbohydrate diet, divided into four meals, and was given 5 units of regular insulin before each meal. Upon

discharge, he was advised to curtail carbohydrates and to eat three meals a day. He was instructed to modify a basic dosage of 10 units of regular insulin before each meal according to the results of urinalyses before each meal. The patient soon began to omit his breakfast insulin because his early morning specimens were consistently sugar-free. He discovered that periodic nervousness an hour after lunch and supper was relieved by reducing his insulin to 5 units before these meals. During May 1943, the patient complained of listlessness and fatigue upon arising. These complaints were frequently associated with early morning headaches. On May 6, 1943, a fasting blood sugar was 45 mg per cent and the urine was sugar free but showed a trace of acetone. The patient was advised to start taking 5 units of insulin before breakfast and to continue with the same dosage before lunch and supper. His complaints continued and on May 30, 1943, a fasting blood sugar was 65 mg per cent. *Again the urine was sugar free but showed a trace of acetone.* The patient was advised to continue taking 5 units of insulin before each meal because of the acetoneuria.

The patient came under my observation during June of 1943 while hospitalized because of acute gonorrheal urethritis. This had completely subsided before I was asked to see the patient because of his purported diabetes mellitus. Physical examination was normal. The patient was placed on a diet of 250 grams of carbohydrate, 80 grams of protein, and 60 grams of fat. No insulin was given. The 24 hour glycosuria amounted to less than 10 grams and usually less than 5 grams. His early morning complaints disappeared immediately. Fasting blood sugars were normal and a carbohydrate tolerance test revealed that this patient's diagnosis was renal glycosuria.

*Dose 100 grams glucose*

Time	Blood Sugar*	Urine Sugar
Fasting	114 mg %	0
$\frac{1}{2}$ hour	167 mg %	Trace
1 hour	145 mg %	Trace
2 hours	130 mg %	Trace
3 hours	92 mg %	0

\* (Capillary blood sugar determinations by the Folin micromethod)

The benign nature of the condition was explained to him and he was discharged with instructions to take no insulin unless further studies indicated need for it.

The failure to appreciate the cause of the ketonuria in this case is illustrated by the fact that in the face of acetonuria per se more insulin was advised. The low blood sugars confirm the impression that the patient was undergoing recurrent hypoglycemia, which were evidenced clinically by the patient's complaints. These comments are independent of the erroneous identification of glycosuria as diabetes mellitus. We may presume that in this individual the ketogenic factors operating in cases of diabetes mellitus could not have been present since we have shown that the carbohydrate tolerance curve was normal. Thus, by eliminating diabetes mellitus as a factor, the causal relationship between hypoglycemia and ketonuria is clearly illustrated.

**Case 4** A 20 year old male patient came under observation during September 1943 because of a number of previous attacks of "blacking out," preceded frequently by automatic behavior. One such attack occurred September 1, 1943 while the patient was marching in a group to a classroom. His companions later told him that he had been marching as if in a daze and then fell to the ground unconscious. There was no convulsion. The family history was negative. The past history revealed that the patient had had pneumonia during childhood, with no sequelae, but



had experienced no other serious illness. At the age of 12, he was hit by a baseball and was unconscious for 10 minutes but recovery was complete.

The physical examination revealed an asthenic individual with no physical abnormalities. Blood pressure was 110 mm Hg systolic and 56 mm diastolic, pulse, 80, weight, 128 lbs, height, 68 inches. An investigation of the patient's personality revealed that he had always been a tense, hyperkinetic individual who worried much over minor matters. Dreams of nightmare proportions were rather frequent. He admitted undue anxiety and tension whenever he was in the foreground and always preferred to remain in the background.

During the course of routine examination, the fasting blood sugar was found to be 65 mg per cent (capillary blood). Blood Kahn reaction was negative. Radiographic studies of the skull revealed no abnormalities. He was subjected to a 24 hour fast, during which time his only complaint was mild frontal headaches and at the end of which time his blood sugar was 72 mg per cent. The patient was then given a general diet for several days before a modified carbohydrate tolerance curve was obtained.

*Dose 50 grams glucose*

Time	Blood Sugar*	Urine	
		Sugar	Acetone
Fasting	74 mg %	0	0
$\frac{1}{2}$ hour	112 mg %	0	0
1 hour	88 mg %	0	0
2 hours	49 mg %	0	0
3 hours	52 mg %	0	0
4 hours	53 mg %	0	0
5 hours	60 mg %	0	0
6 hours	60 mg %	0	Trace
7 hours	52 mg %	0	1 plus

\* (Capillary blood sugar determinations—Folin micromethod)

After the blood sugar level had remained at hypoglycemic levels for five hours acetone began to appear in the urine. Immediately following the seventh hour, the patient became extremely nervous and lost consciousness for a few minutes. He responded promptly to glucose by vein. A diagnosis of spontaneous hypoglycemia was made in the absence of findings pointing to organic disease.

The prolonged hypoglycemia observed during the latter part of the carbohydrate tolerance test resulted in the appearance of acetone in the urine. The patient was prepared for the tolerance test by the administration of a high caloric, high vitamin diet for several days before it was performed. Thus, we attempted to eliminate starvation as a factor in the ketogenesis. It is unfortunate that starvation cannot be conclusively eliminated as a factor because the blood sugar and urine acetone determinations were not made during the 24 hour fast. Nevertheless, it is felt that in this case there was an insulin induced hypoglycemia followed by the appearance of acetonuria, the source of the insulin being endogenous. The initial dose of glucose stimulated an excessive secretion of endogenous insulin and the resultant hypoglycemia in turn brought about the ketonuria. Thus, this case supports further the idea of the causal relationship between insulin induced hypoglycemia and ketonuria.

## DISCUSSION

Collip<sup>6</sup> in 1922 was the first to observe experimentally that rabbits made hypoglycemic by insulin developed ketonuria. Mirsky<sup>1</sup> has pointed out that the older concepts concerning ketogenesis and ketolysis remain as the pre-

vailing point of view of the majority of clinicians. That this is true is demonstrated by the early management of Case 1 and Case 3 in which the appearance of acetone apparently was thought to be the result of the diabetic process and for which additional insulin was administered, whereas the correct interpretation should have dictated the administration of either no insulin or more carbohydrate or both.

Briefly, it is to be pointed out that the ketonuria in all these cases is a readily available clinical reflection of an increased blood ketone level which, in turn, is a reflection of increased fat metabolism in the liver, secondary to hypoglycemia. We do not mean to infer that every hypoglycemic state is followed by ketonuria, but a rise in the blood ketone level can often be demonstrated.<sup>2</sup> When insulin has been given in amounts such as to produce a hypoglycemic state, there is an exaggerated physiologic response which rapidly depletes the liver of its glycogen store. During such phases of glycogen loss, the liver begins to metabolize increasing amounts of fat (and protein). The ketonemic level at any given time depends on four factors which can be readily appreciated on the basis of the following diagram taken from Somogyi.<sup>3</sup>

Ketonemic Level			
Is Increased by		Is Decreased by	
Deglycogenation of liver, entailing an increase in its fat catabolism (Factor I)	Decrease in rate of ketone utilization in extra-hepatic tissues (Factor II)	Increased CHO utilization in liver, which depresses fat catabolism (Factor III)	Increase in rate of ketone utilization in extrahepatic tissues (Factor IV)

That insulin may be either anti-ketogenic or ketogenic is not generally appreciated. The liver of the diabetic patient has a deficient glycogen store because in the diabetic organism glycogenolysis is accelerated. Insulin, in amounts sufficient to halt the glycogenolysis, will be anti-ketogenic since it favors glycogen deposition. Since the liver preferentially metabolizes carbohydrate, the metabolism of fat will decrease as glycogen becomes available. Conversely, following the exhibition of too much insulin, there is an excessive outpouring of glycogen from the liver in an attempt on the part of the organism to correct the hypoglycemic state. As a result of this outpouring of glycogen from the liver, fat metabolism is stepped up, the ketonemic level increases, and in the final analysis insulin has become ketogenic.<sup>2\*</sup>

Four clinical experiences have been reported in which the common denominator is insulin induced hypoglycemia followed by the appearance of ketonuria. In two of the cases it has been pointed out that the failure to recognize the ketogenic potentialities of insulin has resulted in aggravation of the ketonuria. In our experience the combination of aglycosuria and ketonuria has frequently led us to find and correct insulin induced hypo-

\* Mirsky's<sup>1</sup> paper gives a brief exposition of current theories concerning ketogenesis and ketolysis.

glycemias which had been occult. It is obvious that the avoidance of the hypoglycemic state in the diabetic patient is of extreme importance since repeated hypoglycemias will further deplete glycogen stores which are usually subnormal in the newly discovered diabetic organism.

### SUMMARY

Four cases have been presented in which aglycosuria and ketonuria were found following insulin-induced hypoglycemic states. Two of the cases reported were diabetes mellitus, one was a case of renal glycosuria and one was spontaneous (neurogenic) hypoglycemia. This demonstrates that the ketonuria described is not peculiar to diabetes mellitus but is the result of physiologic responses to the hypoglycemic state. The interpretation of this phenomenon has been discussed and its importance with particular reference to the management of diabetic patients has been pointed out.

*Note.* The author wishes to acknowledge gratitude to Dr Michael Somogyi, under whose guidance was kindled an interest in and appreciation of the problems covered by this paper, and to Colonel J. S. Sweeney, M.C., A.U.S., Chief of the Medical Service, Bushnell General Hospital, for his constant encouragement and for his splendid clinical and editorial assistance.

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# PICROTOXIN IN BARBITURATE POISONING <sup>1</sup>

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PICROTOXIN as an antidote for human barbiturate poisoning was used first by Arnett <sup>1</sup> in 1933 Maloney, Fitch and Tatum <sup>2</sup> previously had demonstrated its effectiveness by animal experiments In 1936 Koppanyi and his co-workers <sup>3</sup> definitely established its clinical value and proved its safety when administered properly During the ensuing years the practical use of picrotoxin has been determined, particularly for those patients having a degree of narcosis approaching lethal levels

The recent extensive review of the pharmacologic and physiologic aspects of the barbiturate problem by Tatum <sup>4</sup> and Richards' <sup>5</sup> clinical evaluation of picrotoxin in barbiturate poisoning agree in establishing it as the analeptic of choice in instances of dangerously deep depression There is abundant evidence that other analeptics such as metrazol are effective in the barbiturate poisoned patient, but most of those with experience are in accord with the above authors that from the point of view of safety and sustained effectiveness picrotoxin is preferable <sup>5, 6, 7, 8</sup> However, there still exists in many clinics an overcautious and at times almost unreasonable reluctance to employ this drug Some physicians maintain that most patients suffering from barbiturate poisoning will recover eventually with supportive treatment supplemented by the less potent stimulants This is undoubtedly true in many instances, but unfortunately is not always the case as may be seen by a review of a number of reports

In New York City alone barbiturate suicides approximately doubled in the five year period from 1937 to 1941 <sup>9</sup> A five year study in Connecticut <sup>10</sup> revealed a mortality of 298 or 5.9 per cent in 1780 cases of attempted suicide with barbiturates This includes all cases reported, many of which were not alarmingly narcotized Other sources <sup>5, 10, 11</sup> report 6.5, 7.3, and 6.0 per cent fatalities A mortality rate of over 6 per cent warrants the utilization of every merited therapeutic measure available

The complications accompanying prolonged depression from barbituric acid derivatives cannot be ignored Although some untreated patients recover from excessively large doses as illustrated below, the prolonged period of morbidity with its undesirable complications is to be avoided if possible Prolonged hypoxia, intercurrent pulmonary infection, pulmonary edema, cerebral edema, nutritional deficiencies, depressed kidney function, decubitus ulcers and transient or more permanent neurological sequelae are the more frequent accompaniments of prolonged barbiturate narcosis <sup>5, 11, 12, 13</sup>

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In discussing the advisability of picrotoxin therapy in given cases of poisoning, the impression frequently is gained that either a lack of familiarity with the drug, or a fear of its potency, or both are responsible for the reluctance to use it. To those familiar with its action and the method of administration there is no substantial reason to withhold it from patients for whom its use is indicated. It should be employed early and in adequate amounts supplemented by other supportive measures. The following typical case histories are presented in support of this contention.

### CASE REPORTS

*Case 1* A 30 year old white female reported to have taken about 20 gm of secenal came from another hospital where she had been admitted 24 hours earlier. No active treatment had been instituted although the patient was comatose upon admission. When transferred she was still in deep coma and gave no response to painful stimuli. The temperature was 100.6° F, pulse rate 78, and the blood pressure 100 mm Hg systolic and 72 mm diastolic. She was breathing deeply and regularly at a rate of 12 times per minute. The skin was of good color, warm and moist. Pupillary responses were variable. Both lung fields were filled with scattered rhonchi. Barbituric acid was found in the gastric contents and the urine. The blood concentration was 0.095 gm per 100 cc. Benzedrine, 0.02 gm, was administered on admission followed by caffeine sodium benzoate, 0.5 gm every hour. Sulfadiazine routine was begun nine hours after admission. The only evidence of improvement was an occasional movement of the extremities during a two hour period beginning 10 hours after admission. The temperature gradually rose to 108° F, the pulse rate to 160, and the respiratory rate to 40 per minute. The patient died 15 hours after admission with a terminal picture of pulmonary edema. An autopsy revealed bilateral bronchopneumonia, pulmonary edema of the upper lobes, and slight pial congestion.

This is an example of the too frequent outcome of inadequately treated acute barbiturate poisoning. Although the patient had been comatose for at least 24 hours, her relatively good condition on admission points to the probability that with proper management the case might have terminated differently. Certainly experience suggests that the therapy was inadequate.

*Case 2* A 29 year old white female was admitted to the hospital October 14 approximately 10 hours after taking 50 gm of pentobarbital sodium as was learned from a subsequent history. She was deeply comatose, areflexic and unresponsive to all stimuli. The skin was slightly cyanotic, the pupils variable in size. The temperature was 102.6° F, the pulse rate 112, the blood pressure 96 mm Hg systolic and 54 mm diastolic, and the respiratory rate 28 per minute with shallow and slightly irregular breathing. Urine and gastric contents when analyzed were positive for barbituric acid. Initial therapy included gastric lavage, intravenous thiamine chloride 0.02 gm every six hours, and metrazol, 2 cc hourly, ordered to be given until twitchings or convulsions occurred. Nine hours later breath sounds were absent over the left upper lobe, expansion of the right chest was greater than the left with shallow breathing at a rate of 34 per minute. Breath sounds returned in the left axillary area three hours later, at which time sulfapyridine therapy was begun. Metrazol was continued. Thirty hours after admission the temperature was 105° F, pulse rate 130, respirations 26 per minute. Metrazol, 11 cc, was then given intravenously over a period of 42 minutes, resulting in leg movements, followed two hours later by occasional motion of all extremities and a return of the swallowing reflex. Pain stimuli still elicited no response. Two more intravenous doses of metrazol, 5 cc each, were then given an hour apart after which the analeptic was discontinued. Deep reflexes

returned 40 hours after admission with some spontaneous movements. Response to stimulation was absent until the fourth day, at which time left lower lobar pneumonia developed and the cough reflex appeared. The patient's condition remained essentially unchanged for three succeeding days, when the temperature began to fall and the lungs became less congested. At this time more vigorous vitamin therapy was instituted. Bullae which had appeared on the heels became infected and ulcerated. On October 21 the patient became more active. Two days later, nine days after admission, verbal contact was established and she awakened sluggishly. At this time a left foot drop was noticed. Following a slow convalescence the patient was discharged on November 23. Six days later she returned, was rehospitalized for two weeks, and then sent to a rest home for two months. At the end of this time the foot drop persisted, causing the patient considerable concern for fear that it would interfere with rehabilitation. Total hospitalization was 68 days, plus an additional and incomplete convalescence of two months.

The prolonged recovery time, the slow convalescence and the unfortunate sequelae suggest that one error in management was the postponement of adequate analeptic therapy. Thirty hours elapsed before the return of reflexes and motor activity, during which time pulmonary disease became established and the groundwork laid for other complications. Stimulants sufficient to establish and maintain reflexes and active movements are indicated as early therapy in every case.

*Case 3* A 43 year old white female was admitted on April 4, 24 hours after ingestion of 4.25 gm of pentobarbital sodium. Urinalysis revealed barbituric acid, 0.026 gm per 100 c.c. During the first 18 hours of treatment she was given intravenous fluids, coramine, 15 c.c., and caffeine sodium benzoate, 10 gm. The treatment was then undertaken by another service. The patient was deeply comatose, slightly cyanotic and areflexic. The face was edematous. Temperature was 102.8° F, the pulse rate 120 and of a thready character. The breathing was a shallow type at a rate of 15 per minute and there were moist râles at both lung bases. Oropharyngeal oxygen by nasal catheter was ordered and intravenous picROTOXIN was administered at the rate of 0.003 gm per minute until 0.024 gm was given. The patient then began to yawn, respirations increased in rate and depth, and the corneal and plantar reflexes returned. During the next 12 hours picROTOXIN was given intramuscularly in 0.003 gm doses every half hour, except once when depression deepened and 0.012 gm was given intravenously. This was followed by active movements and occasional moans. Analeptic therapy was discontinued for 13 hours when deep narcosis again appeared. PicROTOXIN, intramuscularly, was resumed in 0.003 gm doses every half hour for the next nine hours, with one episode of regression when it was administered intravenously. A total of 0.238 gm was used over this 36 hour period. Adequate intravenous fluids and vitamin therapy were maintained throughout. The patient became increasingly active, finally requiring restraints. Bullae of the ankles and legs demanded special care. Approximately 92 hours after taking the drug, the patient showed signs of awakening, and 12 hours later recognized her family. When fully conscious the patient complained of blurred vision, tingling of the hands and feet, and a sluggish memory. These symptoms decreased during convalescence, but were present in a minimal degree upon discharge on April 26.

Though delayed, the effectiveness of picROTOXIN therapy is demonstrated by this report. Such treatment should be instituted at the earliest possible moment. Had it been done in this instance, experience with other cases warrants the conjecture that the result would have been more satisfactory. This is borne out also by the following history.

*Case 4* A 27 year old white female was admitted at 5:30 a.m. in deep coma. Information was volunteered that she probably had taken pentobarbital sodium. This was confirmed subsequently, the amount being 9.0 gm seven and one-half hours before

admission. Respirations ceased as the patient was brought into the emergency room. The skin was cyanotic and clammy, the pulse barely perceptible at 88 per minute, the rectal temperature was 98.6° F. Reflexes were absent, the eyeballs motionless, and the pupils moderately constricted. Two ampules of coramine intravenously and three intramuscularly produced a temporary slow, shallow breathing of three minutes' duration. Artificial respiration was instituted. A nasoendotracheal tube was inserted and the patient placed in a respirator. The cyanosis disappeared and the pulse improved in quality. Oxygen by catheter and intravenous glucose-saline were started followed by gastric lavage. Momentarily stopping the respirator caused reappearance of cyanosis with no evidence of spontaneous respiration. The areflexia persisted. The temperature gradually rose to 103.4° F and the pulse to 120 during the next eight hours. After 12 hours without improvement, intravenous picrotoxin was started at the rate of 0.003 gm per minute. Twenty-three minutes later after 0.06 gm was given, slight twitchings of the eyelids and facial muscles began rapidly spreading to the shoulders and upper extremities. Picrotoxin was discontinued and the convulsive movements ceased. The corneal reflex returned but apnea persisted. An additional 0.012 gm of picrotoxin was given intravenously and 40 minutes after initiation of analeptic therapy, the patient gave a deep sigh and resumed breathing. The rate was 28 per minute, the excursions normal. Picrotoxin was continued intramuscularly, 0.003 gm every 15 to 30 minutes as indicated for the next five hours except twice when extremely shallow respirations responded promptly to intravenous therapy. At 12.30 a.m. all reflexes were present and the patient opened her eyes occasionally. Picrotoxin was discontinued, a total of 0.192 gm having been given. At 3.30 a.m. the endotracheal airway was removed and one hour later, 24 hours after admission, the patient was awake. At 10.30 a.m. she sat up for a chest roentgen-ray and requested breakfast. The temperature was 100.8° F, pulse 100, respirations 24. Convalescence was uneventful and rapid. When interviewed three weeks later there was no evidence of inadequate recovery.

This patient on admission presented a picture similar to the other cases cited plus an added apnea which as far as can be determined is the only recorded case of complete respiratory arrest in acute barbiturate poisoning<sup>14</sup>. Supportive treatment for the first 12 hours was more nearly adequate and much more complete than was given to the other patients cited in this report. The duration of narcosis might have been less had analeptic measures been instituted immediately. However, the result was satisfactory.

Reviewing these four selected cases one notes that upon hospitalization their respective conditions were essentially similar. The effectiveness of the treatment employed for the patient in Case 4 suggests that the others were inadequately managed. It raised the question also whether more favorable results would have been possible had different therapy been employed. Furthermore, the fact that the amount of drug taken by the patient who died was four and one-half times less than in the case which recovered rapidly and completely, even though in the latter narcotization was of a degree sufficient to produce complete respiratory depression adds to the contention that analeptic therapy is imperative. The importance of the time factor is demonstrated also. Postponing treatment as was done in Case 3, and the failure to employ adequate quantities of an analeptic possessing maximum sustaining qualities for the patient in Case 2 surely contributed to the prolonged morbidity and unsatisfactory recoveries.

It is a foregone conclusion that the patient suffering from deep barbiturate depression should be afforded every advantage favoring rapid and complete recovery. The following régime summarizes the accepted procedures essential to proper handling of such cases. The condition of the patient when first seen and the response to therapy is, of course, to be used as an index in each individual instance.

1 *An adequate airway* must be established immediately and maintained throughout. Oropharyngeal toilet to remove all secretions is best accomplished by suction, to be repeated whenever necessary. A nasoendotracheal airway is always indicated for the comatose patient in whom cough and swallowing reflexes are absent. This affords both an unobstructed airway and a means for aspiration. The airway must be kept clear of secretions by catheter suction. Such suction is employed routinely every hour if no evidence of occlusion is present, more frequently if indicated. The suction catheter must be inserted to the distal end of the airway to insure against a gradual occlusion from deposition of secretions along its walls. The endotracheal tube is left in place until resumption of a vigorous cough reflex, which may occur in a relatively short time or which may not reappear for several days if analeptic therapy is delayed. The anesthetist must remove, clean and replace the tube regularly at intervals of not less than 12 hours. When the airway is removed, if signs of laryngeal edema appear, it must be replaced at once. This is a rare complication and occurs within 30 minutes, if at all. When reflexes are sufficiently active to prevent intubation, postural drainage is maintained by elevation of the foot of the bed. The necessity for frequent turning of the patient needs no explanation.

2 *Artificial respiration* may be necessary in bradypnea or when very shallow respiratory excursions are present. This is not usually required for any prolonged period if analeptic therapy is not delayed.

3 *Oxygen* by a properly placed, correct type of oropharyngeal catheter at a flow of six liters per minute affords an adequate concentration at the alveoli.<sup>12</sup> This combats existing hypoxia and prevents its continuation. The catheter must be kept free of secretions at all times. If an endotracheal tube is in place a No. 12 French catheter is inserted into it to a depth of 5 cm without interference with respiratory exchange. A properly fitted mask may be used if desired. The combination flow-meter positive-pressure mask is preferred, permitting an accurate control of oxygen percentage and making possible immediate application of positive pressure should pulmonary edema develop.

4 *Gastric lavage* is performed to remove any remaining drug and to empty the atonic stomach. The contents are analyzed for barbiturate. Catharsis is advocated in some clinics, leaving 300 cc of sodium sulfate in the stomach for this purpose. The possibility of regurgitation and aspiration of gastric contents is a real danger in an unintubated, comatose patient, hence it is preferable to have the stomach completely empty rather than risk this complication. Tube feeding is condemned for the same reason.



5 *Analeptic therapy* should be conservative if reflexes are active and motor activity present. Vigorous treatment is for the deeply depressed patient. In such cases picrotoxin may be given in 0.001 to 0.003 gm doses intravenously, or in 0.003 to 0.006 gm doses intramuscularly every 15 minutes until the desired response is attained. This fractional method is not so effective as the continuous intravenous procedure, which is equally safe if employed with proper caution. The drug is administered at the rate of 0.001 to 0.002 gm per minute until the corneal, swallowing or other reflexes appear, or until slight twitchings of the facial muscles occur. If given beyond this point convulsions may result. These usually are of a mild nature and gradually subside as the stimulant is destroyed. Should they be severe, or should milder ones maintain, an intravenous barbiturate such as sodium pentothal is given slowly just to the point of control. Once signs of reflex and motor activity return picrotoxin is continued intramuscularly in maintenance doses of 0.003 to 0.006 gm each 15 to 30 minutes as indicated. Should regression develop the same dose is given intravenously until the desired plane of activity is reestablished. Each case must be treated individually and the drug continued until active reflexes and involuntary movements are maintained.

Since the action of picrotoxin may be delayed for as much as 10 minutes, caution is to be exercised in its administration. Furthermore, the impression has been gained that the initial response to picrotoxin following depression from the longer acting barbiturates is slower than is the case with the shorter acting ones, hence the analeptic should be given in smaller amounts if its accumulation with a resultant sudden and severe stimulation is to be avoided. Convulsions, if they occur, usually are followed by a degree of depression deeper than that existing before their onset.

The amount of picrotoxin necessary to establish the desired plane of activity is unpredictable. The wide variation in dosage seemingly bears little relation to the quantity of barbiturate taken. Although 0.02 gm of picrotoxin is dangerously toxic to a normal adult,<sup>16</sup> doses ranging from 1.079 to 2.296 gm have been employed for patients poisoned by barbituric acid derivatives.<sup>17, 5</sup>

6 *Intravenous fluid therapy* should not be delayed. Not only does this afford a route for the administration of analeptics, but insures proper hydration and nourishment and enhances renal function. Should prolonged venoclysis be necessary, adjustment to the needs of the individual patient is most important. Fluids must be administered judiciously if pulmonary edema is to be avoided. Two liters of 5 per cent glucose in normal saline with 1 liter of 5 per cent glucose in water given slowly meet the 24 hour requirements of the average patient.

Prolonged coma demands special attention to needs other than fluid and carbohydrate requirements and electrolyte balance. A positive nitrogen balance is maintained by intravenous amino acid therapy with an average dose of 70 gm per day. This can be given separately in a 5 to 10 per cent solu-

tion or mixed with the glucose-saline infusion To avoid urinary spill the rate of flow should be adjusted to not more than 20 gm, preferably less, in two hours, the total amount being divided into three equal portions started at eight hour intervals The amino acids are utilized by the body for protein synthesis, sparing the body tissues against breakdown for energy production<sup>18, 19</sup>

Vitamin therapy is indispensable if normal metabolism is to be approximated and neurological complications prevented in the patient who remains comatose for more than 24 hours Parenteral thiamine chloride 0.005 gm, riboflavin 0.005 gm, and nicotinic acid 0.05 gm given three times daily afford an adequate quantity of the B complex They may be given in combined form Sufficient vitamin C is insured by 0.10 gm of ascorbic or cevitamic acid daily In addition to its usual functions, Richards<sup>20</sup> demonstrated that vitamin C shortens the narcosis induced by the shorter acting barbiturates such as nembutal

Circulatory collapse, should it appear, requires prompt antishock therapy with adequate amounts of plasma and the other supportive measures usually employed

7 *Chemotherapy* is instituted should signs of pneumonia or other intercurrent infection appear Pneumonia may be hypostatic, lobar or from aspiration Early stimulation therapy, properly controlled fluid intake, and the prevention of aspiration usually will prove prophylactic against pneumonia, pulmonary edema or pulmonary abscess development

8 *Duresis* may be enhanced by intravenous fluids and diuretics should depression of urinary output occur Many patients are incontinent, although others may require catheterization every 10 hours to prevent bladder distention and to be certain that kidney function is adequate

9 *Nursing care* must be of the best with constant attention to all details, if good results are to be obtained Oral hygiene, padding of pressure points to avoid decubitus, protection of the frequently appearing bullae, reduction of marked hyperthermia and protection of the patient against injuries once motor activity is resumed warrant special emphasis Once consciousness returns psychiatric problems may arise which will require expert handling by both the physician and nurse

## SUMMARY

The therapy of barbiturate intoxication is an increasingly important problem confronting the medical profession There is a hesitancy on the part of some to employ the more potent analeptics and to institute certain other supportive therapies available Four cases essentially similar are presented to illustrate the effects of neglected, inadequate, delayed and more immediate treatment A suggested therapeutic régime is outlined Early and adequate analeptic therapy with picrotoxin may prevent death, obviate a prolonged illness and result in a complete or more nearly complete recovery Each case must be judged by the condition of the patient when admitted to

the hospital and managed according to the response shown toward undelayed treatment. If this is prompt, the more expensive and time consuming measures should not be necessary.

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# DEMONSTRATION OF VISCERAL PAIN BY DETERMINATION OF SKIN POTENTIALS \*

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THE need of a method that permits one to demonstrate and to localize pain objectively in disease of internal organs is particularly striking under conditions such as the present national emergency. Every day the physician is confronted by the question as to whether the complaint of pain in a certain area is caused by an organic disease or whether it is of a psychic nature.

The need for an objective "pain-detector" is at least partly met by the measurements of the so-called viscerogalvanic reaction (Spiegel and Wohl). These authors studied the electrical potentials of the skin in cases of visceral pain and often found increase of these potentials in the area corresponding to the diseased organ. They explained the reaction due to reflex excitation of the sweat glands in the respective dermatomes, an excitation that is sustained by continuous impulses from the pathologic viscus. These studies were confirmed by findings of Guttmann who demonstrated colorimetrically, in cases of gall-bladder disease, disturbances of the sweat secretion in the corresponding dermatomes by the chinizarin method †.

In the present study we tried to ascertain whether the viscerogalvanic reaction may be an aid in the differential diagnosis between pain in organic visceral disease and that in non-organic disorders.

*Method* The method is that used by Spiegel and Wohl with further modifications. A known variable potential is opposed to the unknown skin potential (compensation method figure 1). The known potential is varied until both potentials are equal, so that a zero instrument (string galvanometer, Leeds and Northrup portable galvanometer) shows no deflection. The principle is similar to that used in electrocardiography when the skin potentials are neutralized. In fact, the neutralizer of an electrocardiograph can be used for this purpose, if one standardizes its various positions in millivolts. Zinc-zinc sulfate electrodes were used as nonpolarisable electrodes. An amalgamated zinc rod dips into a glass tube I containing a saturated zinc sulfate solution (figure 2). The lower end of tube I is closed by a cellophane membrane separating it from a normal KCl or physiologic saline solution that is contained in a second glass tube. The lower end of glass tube II is also closed by a cellophane membrane, it is

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† Recently Portnoy found a positive viscerogalvanic reaction in 70 per cent of the cases of visceral pain studied.

to be applied to the skin. The testing electrode which is held by a handle is counterbalanced by a weight, so that it can be applied to the various areas to be tested with minimum pressure. This is important because pressure reduces or distorts the skin potentials. The indifferent electrode fits into a holder that can be strapped to the dorsal aspect of the forearm under con-

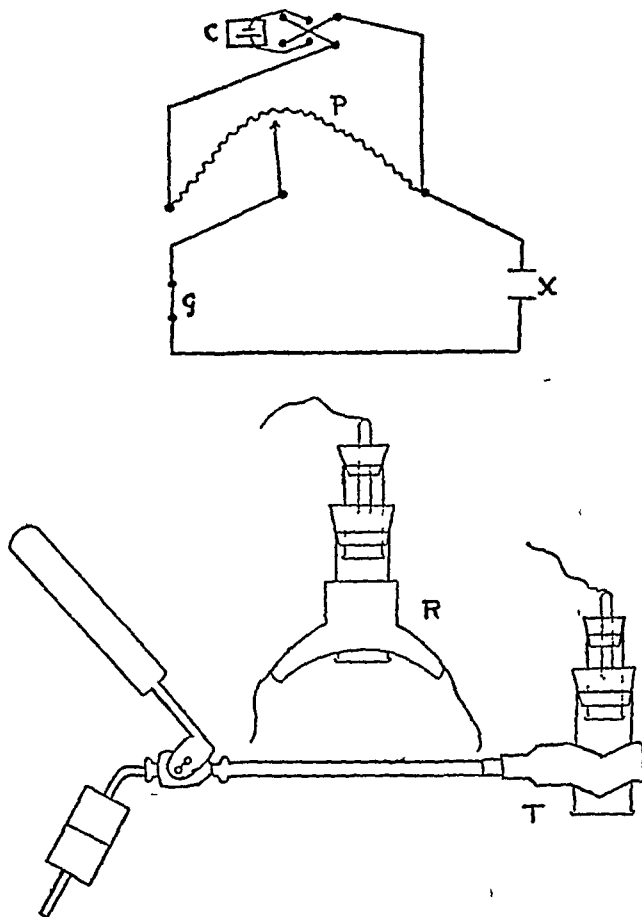


FIG 1a (above) Principle of compensation method

C—dry cell, G—galvanometer, P—potentiometer, X—unknown skin potential

FIG 1b (below) Unpolarisable electrodes

T—testing electrode, R—reference electrode

stant pressure so that the reference point has as low a potential as possible. Other measures which contribute toward successful results are (1) the patients should be kept relaxed in a recumbent position in a warm room, (2) the testing electrode should be applied to each area for about the same length of time, (3) the testing electrode should be kept away, insofar as possible, from direct application to a hairy area, (4) excessively hairy areas should be shaved first and the testing done three or more days later.

*Material* A series of 62 patients and 10 healthy, asymptomatic subjects was tested, making a total of 72 subjects.

In group I were 31 cases with pain accompanying proved organic disease (tables 1 and 2) \*

The diagnosis was established after complete digestive tract studies were made, in addition to the history and physical examination, including gastrointestinal roentgen-ray series, cholecystograms, barium enema, blood Wassermann reaction, blood count and urinalysis. In certain cases, additional studies were carried out such as electrocardiography, gastroscopy, gastric analysis and biliary drainage. In this group are also included four cases

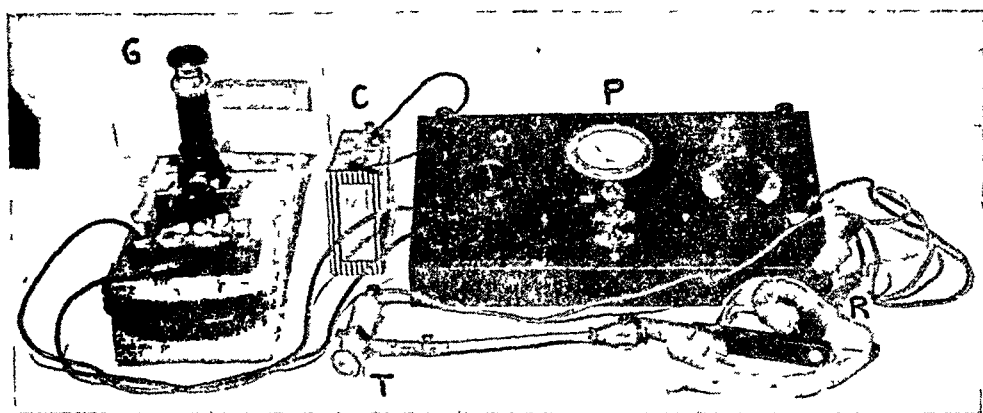


FIG 2 Arrangement of apparatus

C—dry cell, G—galvanometer, P—compensating circuit with potentiometer, R—reference electrode, T—testing electrode

whose primary illness was a colitis (non-ulcerative, non-specific). Although these cases were non-ulcerative and non-specific and are generally recognized as being "functional" in nature, they were included in this group since, besides roentgen-ray findings such as loss of normal haustral markings, "string sign" or marked spasticity or irritability, definite inflammatory signs were present on proctosigmoidoscopy, such as edema of the mucosa, congestion, abnormal friability and bleeding of the mucosa. In cases 1 and 17, in which chronic gastritis was present, the diagnosis was arrived at after gastroscopic examination in addition to the roentgen-ray and gastric analysis studies.

Group II comprised 27 cases and consisted of patients suffering from such disturbances as neuroses, of whom there were 13 cases, and patients, who were symptom-free, but had had some organic disease at a previous date (table 3). In the group of patients with neuroses, vague aches and pains were complained of. These non-characteristic distress symptoms were judged to be of psychic origin from the historical and physical findings, as well as the roentgen-ray and laboratory findings.

Finally, four patients were studied in whom organic disease had recently existed (from three to six months prior to testing date), who were symptom-free for several months, but still showed abnormal skin potentials (table 4).

\* In order to save space the tables have been omitted, but they will be included in the reprints.

*Results* In 10 normal individuals the potential measurement on trunk and extremities except fingers varied between zero and five millivolts \*. Our pathological observations are recorded in tables 1-4. It seems advisable to differentiate the areas tested into two groups. First, the areas where pain is felt (or the dermatomes corresponding to the diseased organ) may be called the P (pain) areas. Second, the remainder of the body surface may be called the R (remainder) areas. The difference D between the maximum potentials of the P (pain) area and R (remainder) area is indicated in each case in tables 1-3.

Among 31 patients with pain accompanying organic visceral disease (tables 1, 2), we find 23 with D values of 10 mv or above 10, nine of these cases had 20 mv or more. In contrast, among 27 patients without demonstrable organic disease (table 3), in no case was a D value of 10 mv or over found. In two cases D values of 8 and 9 mv respectively were observed,† while in the other patients in this same group D was 0 mv. Thus, if D values of 10 mv or above are recorded, such observation may aid in the differential diagnosis between organic visceral pain and pain of non-organic nature such as "psychic" pain, in that it may support the assumption of an organic visceral lesion. However, in some cases, D values below 10 mv may be observed in organic visceral pain as well as in non-organic pain.

The fact that in a number of cases of organic visceral pain a definite increase of skin potential in the respective dermatomes failed to appear is not surprising. It should be borne in mind that reflex effects upon vegetative organs such as the sweat glands depend not only on the intensity of the afferent impulses, but also upon the state of excitability of the vegetative effector organs. It seems that under certain conditions the pathologic afferent impulses are even able to inhibit the activity of the sweat glands, as demonstrated by a case of gall-bladder disease recorded by Guttman. Consequently, diagnostic conclusions should not be drawn from negative results of the viscerogalvanic reaction, the lack of increase of skin potentials does not exclude an organic visceral lesion. Only positive results should be regarded as useful in that they indicate an organic visceral disease if the D value exceeds 10 mv.

Of special interest are the observations that are summarized in table 4. These are cases of organic visceral disease that were clinically "healed" or in a latent stage. The respective dermatomes showed increased potentials as compared with the rest of the body (D values in two cases were 10 and 13 mv respectively and 7 mv in two other cases). These findings indicate that after apparent healing from a clinical point of view, abnormal impulses

\* Face, palm of hand, sole of the foot normally may show high potentials and, therefore, were usually not measured.

† The finding of potential differences in these cases is perhaps due to instability of the reference point. As pointed out by Snodgrass, Rock and Menkin in their study of ovulation potentials, emotional factors may cause such an instability, but this is insufficient to place the readings within the range of organic disease values.

may still originate in the respective organ or in scar tissue within or around the affected organ and may still maintain, at least for some time, a tonic excitation of segmental centers of the spinal cord, although these impulses may be below the threshold of the higher centers upon which conscious pain sensation depends

### SUMMARY

1 The study of skin potentials is an objective method useful in the evaluation of visceral pain in 74 per cent of the 31 cases with pain accompanying proved organic visceral disease, there was an increase of the skin potentials in the respective dermatomes over the remainder of the body by 10 or more millivolts

2 Twenty-seven cases with pain of psychogenic origin or healed organic disease revealed two single instances showing potential increases of 8 and 9 millivolts respectively, while the other 25 cases gave no increase of potentials

3 Increase of skin potentials by 10 mv or over in the dermatomes corresponding to an organ causing pain supports the assumption of organic disease. Lack of increased potentials does not exclude organic disease

4 After apparent clinical healing of organic visceral disease, increased potentials may still persist indicating latent pathological changes

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# HYPERVITAMINEMIA A IN THE RECOVERY STAGE OF VARIOUS DISEASES<sup>1</sup>

By F STEIGMANN, M S, M D, F A C P, K A MEYER, M D, F A C S,  
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VARIOUS investigators have found that following a transitory stage of hypo- or avitaminemia-A at the height of the disease the blood vitamin A level rises in the convalescent stage to higher levels than normal and returns to the normal level some time after complete recovery. Such behavior has been described in the convalescent stage of acute hepatitis,<sup>1, 2, 3, 4</sup> in the recovery stage of pneumonia,<sup>2, 3, 4, 5</sup> and in febrile conditions<sup>4, 6, 7</sup>. Since this occurrence appeared of clinical interest, the present study was undertaken to determine the incidence, significance and specificity of this phenomenon and its relation to liver function and to the response of the plasma vitamin A level to the intake of 75,000 units of vitamin A (tolerance curve).

## MATERIAL AND METHOD

This study is based on observations on 35 patients who had at least temporarily a plasma vitamin A level above 50 micrograms and who were selected from a group of 189 patients of a charity hospital on whom serial plasma vitamin A determinations were made. The control cases of this group are composed of patients with hernia, fracture, compensated cardiac conditions and arthritis. They had an average plasma vitamin A level of 32 micrograms/100 c c. Hence, a plasma vitamin A level of above 50 micrograms was assumed to be higher than normal, especially since many of the above mentioned patients were suffering from diseases characterized by a low or zero plasma vitamin A level during their height. Not included in this group are patients with elevated plasma vitamin A level following ingestion of large doses of vitamin A and patients with nephritis, the latter being discussed in another publication.<sup>8</sup>

Many of the selected patients had low or zero plasma vitamin A levels when their observation began. Some of them had plasma vitamin A levels within normal ranges at the start of the study. However, they were already in an improving stage of a disease in which low plasma vitamin A levels are characteristically present during its height. Others were in the convalescing stage of the disease, with plasma vitamin A levels much above

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the normal Determinations of the plasma vitamin A level were done at one to three day intervals over a period of one week to three months depending upon the time when the blood level returned to within normal ranges or upon the time when the patient left our observation

The determinations of plasma vitamin A and carotene were done by means of the Carr-Price reaction according to the method of Kimble<sup>9</sup> The readings were made either by means of the Sheard-Sanford photometer or the Coleman spectrophotometer or by copper sulfate standards according to a modification<sup>10</sup> of the method of Josephs<sup>11</sup> The three methods checked satisfactorily The values were given in micrograms per 100 c c plasma The tolerance curves were performed by determining the plasma vitamin A level before, and 3, 6 and 24 hours after the administration of 75,000 I U of vitamin A esters\* in 2 c c corn oil In some of the patients the following determinations were made to evaluate hepatic function Total cholesterol, cholesterol esters, hippuric acid excretion, cephalin-cholesterol flocculation test and albumin/globulin ratio

## RESULTS

The greatest number of the 35 patients with hypervitaminemia studied had various types of liver diseases (table 1) In them the greatest difference between previous levels and the highest plasma vitamin A level was encountered Less marked was this difference in pneumonia, and postoperative

TABLE I  
Tabulation of Patients in Whom Transient Hypervitaminemia A Was Observed

Diagnosis	No Cases	Average No of Determinations	Average Level in Hypervitaminemia Stage (Micrograms per 100 c c Plasma)	Maximal Difference Encountered in Plasma Vitamin A Levels
Arthritis	1	10	67	14
Fractures	2	10	57	23
Post-operative	3	8	83	72
Obstetrical	9	3	58	52
Pneumonia	2	10	69	69
Cirrhosis	7	11	82	117
Hepatitis	8	8	93	113
Incomplete Obstruction	3	8	71	67

or postpartum conditions The difference in the vitamin A levels in one case with arthritis or two with fractures was less significant, especially since they were found among eight cases of arthritis and among 20 cases of fracture studied

The stage of the disease in which hypervitaminemia-A occurs is demonstrated by the serial determinations of the plasma vitamin A level In

\* Distilled vitamin A concentrate (natural ester form distilled from fish liver and vegetable oil) containing 200,000 USP XI units per gram, generously supplied by Distillation Products, Inc, Rochester, N Y

patients with acute hepatitis, the hypervitaminemia stage occurs at the time when the icterus index returns to normal levels, i e, in the beginning of the convalescent period, when the patient is cured, the plasma vitamin A level returns to normal (figure 1) Some cases of acute hepatitis came under our observation during the recovery period and the liver function tests were already normal In these the plasma vitamin A level was rising at a time

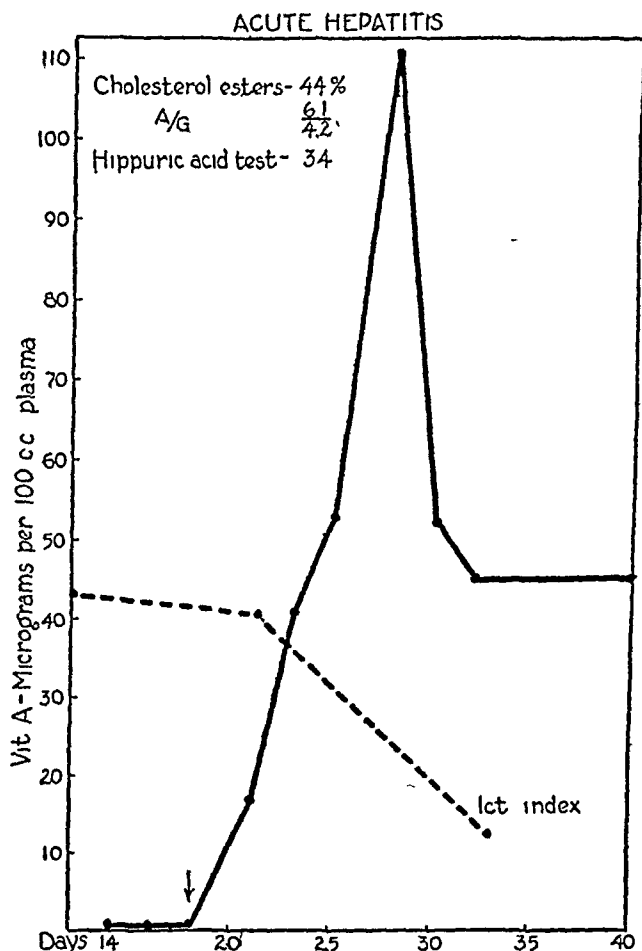


FIG 1

when the icterus index was returning to normal (figure 2) In cirrhosis a similar situation may be encountered with the difference that the period of hypervitaminemia A may be extended for long periods (figure 3) The hypervitaminemia A stage may even occur repeatedly (figure 4)

A similar situation was observed in patients with pneumonia in whom the plasma vitamin A level rose during recovery at about the eighth day of the disease (figure 5) Since these patients left the hospital relatively soon after the acute stage, we do not know when the plasma vitamin A level returned to normal Similar tendencies in the plasma vitamin A level to rise above

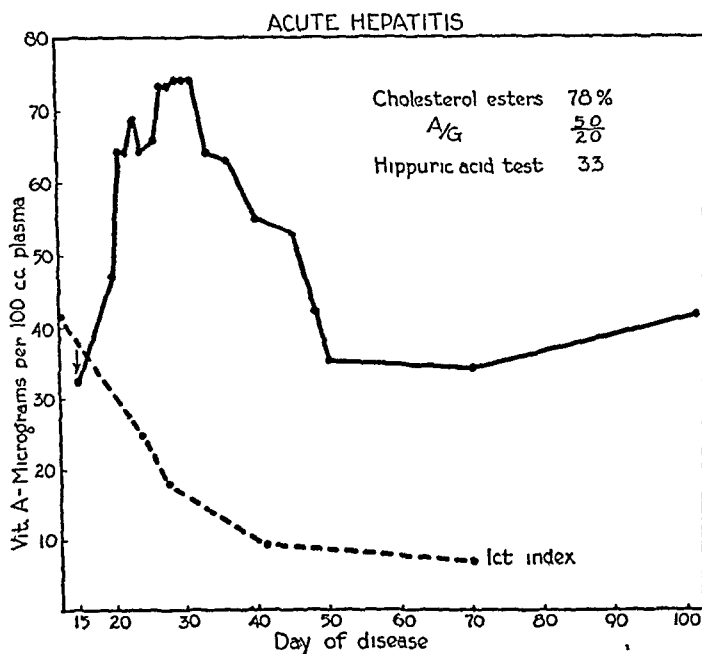


FIG 2

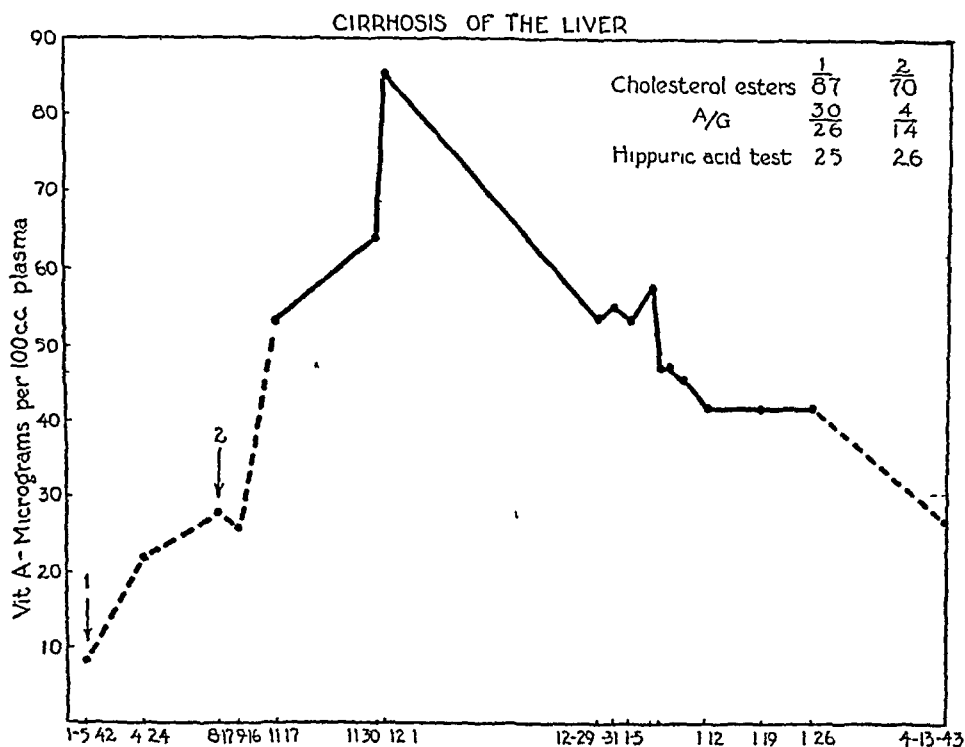


FIG 3

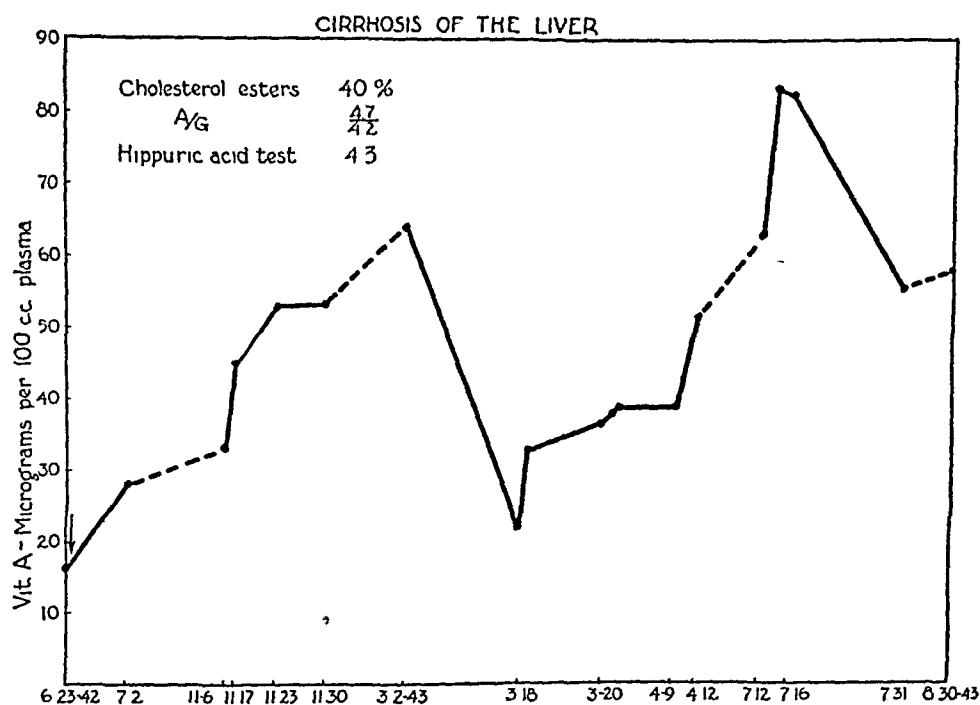


FIG 4

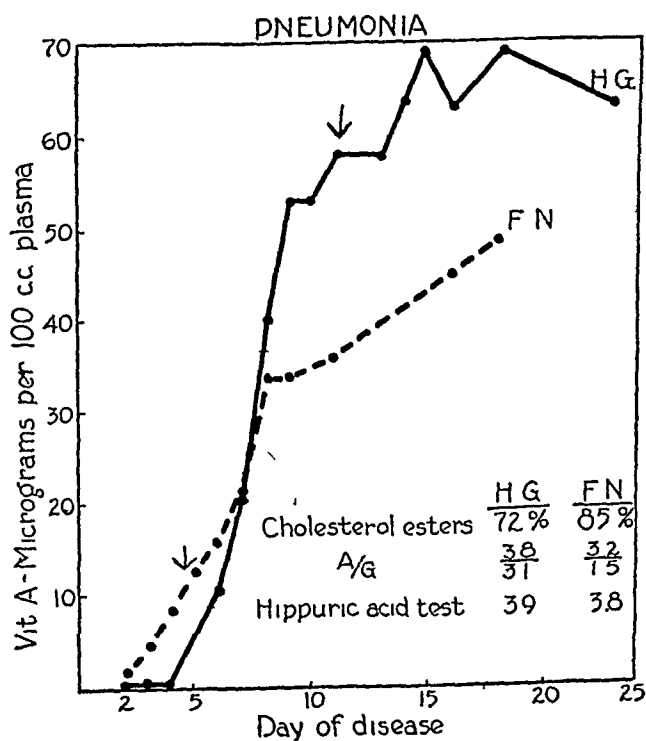


FIG 5

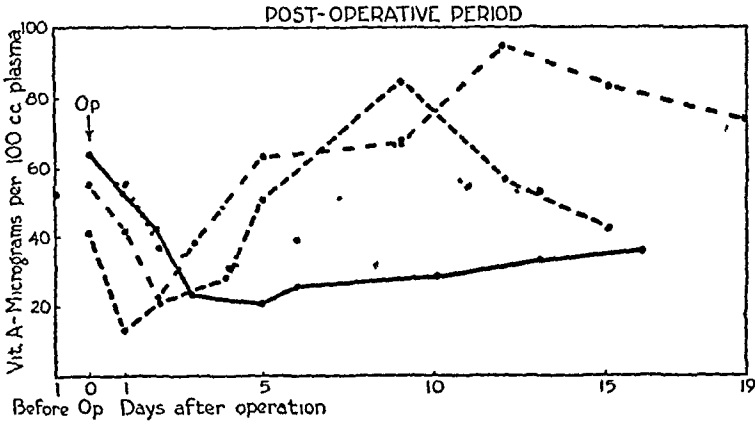


FIG 6

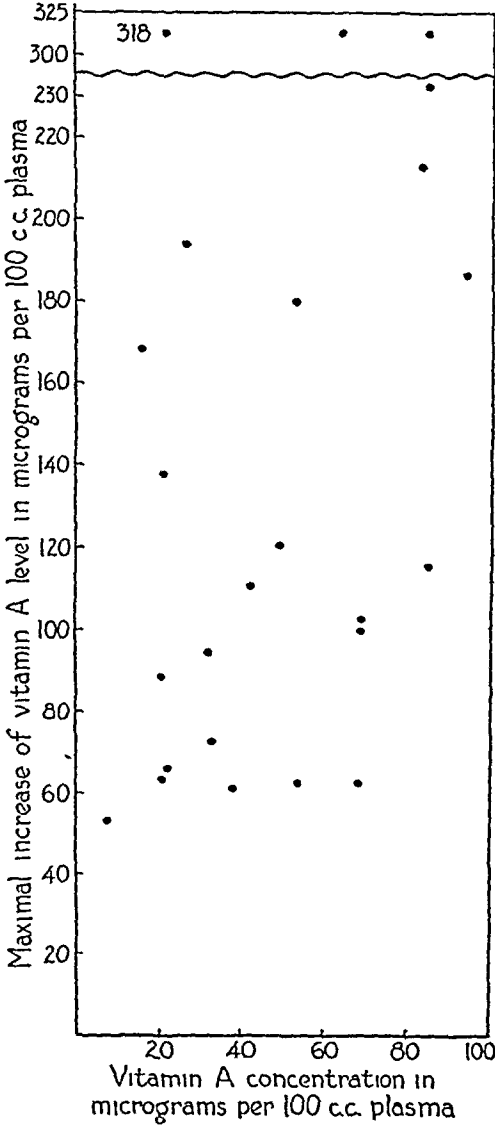


FIG 7

the normal following the initial drop were observed in patients following extensive abdominal operations. The hypovitaminemic stage was observed within 72 hours, and the hypervitaminemic stage was seen at about the tenth day (figure 6).

From the few representative cases in figures 1, 2, 3, 4 in which arrows point to the date when liver function tests were performed, it appears that the liver functions were normal when the plasma vitamin A levels were returning to the normal ranges. The results of the cholesterol esters partition and total plasma protein determination in these patients at different plasma vitamin A levels show that the percentage of cholesterol esters and the total plasma protein increase progressively with a rise in the plasma vitamin A level (table 2). In figure 7 the maximal increase in the tolerance curve is plotted against the plasma vitamin A level. From it a tendency toward higher tolerance curves in the hypervitaminemic stage seems to be apparent.

TABLE II

Comparison of the Plasma Vitamin A Level with the Percentage of Cholesterol Esters and the Total Plasma Protein Concentration

Vitamin A Level Micrograms Per Cent	Cholesterol Esters Percentage	Total Plasma Protein Grams Per Cent
0 to 20	55	6.5
21 to 50	73	6.8
50+	72	7.7

## DISCUSSION

The presented data indicate that marked changes of the plasma vitamin A level may occur which are independent of the nutritional intake. There is no reason to believe that such abrupt changes in the plasma vitamin A level should occur from variations in nutrition which are of a comparatively moderate degree and short duration as seen, for instance, in acute hepatitis, pneumonia, or during operation. We must assume, therefore, that processes within the body govern the plasma vitamin A level.<sup>4</sup> The significance of endogenous in contrast to nutritional factors in the development of conditioned vitamin A deficiency has recently been stressed.<sup>12</sup>

The endogenous forces causing these changes seem to be multifold. Clausen et al.<sup>13</sup> were of the opinion that in the convalescent stage the intestinal absorption, which was impaired during the height of the disease, was already improved whereas the storage ability of the liver was still impaired, thus disturbing the normal balance between absorption and deposition in the liver. Liver function impairment is doubtless the cause of the reduction of the plasma vitamin A level but no indications from the liver function tests were obtained which would suggest that it is responsible for the hypervitaminemia A. The fact that the plasma vitamin A level rises abruptly during the beginning of improvement in cases of hepatitis or pneumonia, at a time when the diet of either is essentially high in protein and carbohydrate and low in fat, would point more to a sudden release of vitamin A.

from the liver into the blood stream rather than to increased absorption. We <sup>4, 14</sup> suggested the possibility that the hypervitaminemia A is due to an increased release of vitamin A from the liver where it was retained in pathologic sites from which it cannot be utilized during the height of the disease <sup>15, 10, 16</sup>. For this fact speaks also the observation that in the acute stage of pneumonia or acute hepatitis the liver stores are not necessarily reduced <sup>3, 17, 18, 19, 20</sup>. A possibility of disturbed liver function with consequent displacement of the liver vitamin A in the acute stages and release during recovery stage can be assumed for other conditions than pneumonia and hepatitis. Furthermore, the observations of Josephs <sup>5</sup> that in infants below two years of age this hypervitaminemia is not as marked, which he explains on the lower available liver vitamin A depots in this age group, is one more evidence for liver release. Lund and Kimble presented evidence for a similar phenomenon in parturient women <sup>21</sup>.

However, the fact that the response of the vitamin A level to the intake of high doses of vitamin A is higher during the hypervitaminemic stage points to the existence of other factors, especially if we exclude liver damage with associated inability to store vitamin A as one of the causes of hypervitaminemia. An improved function of the intestinal tract is probably not the cause. An increased ability of the blood to carry vitamin A or a reduced destruction of vitamin A might be considered as has been done for conditions in renal disease <sup>8</sup>. Recent studies on the anti-oxidative activity of tocopherol (vitamin E), <sup>22, 23, 24</sup> which acts as a co-vitamin, has focused the interest upon processes which protect or destroy vitamin A in the body.

The hypervitaminemia A is not specific for any one disease and it could thus be an unspecific reaction of the body to a previous hypovitaminotic phase without any relation to the nature of the disease, a possibility which Josephs <sup>5</sup> pointed out and associated with the difference in adjustment to vitamin A intake in the hypovitaminotic stage. It was also observed <sup>25</sup> that the blood vitamin A level of normal adults rises to supernormal levels after a period of vitamin A depletion with consequent low vitamin A levels.

Whatever the cause of this phenomenon, it undoubtedly indicates a good prognosis inasmuch as it suggests that the patient is on the road to recovery.

#### SUMMARY AND CONCLUSION

The occurrence of a phase with hypervitaminemia A in various diseases is discussed. This phenomenon is due to endogenous factors and not to nutritional change.

One of these factors seems to be an increased release of vitamin A from pathologic sites in the liver to which it was shifted during the acute stage of the disease. Other factors appear to be increased ability of the blood to hold vitamin A or reduced destruction of vitamin A. Finally, a non-specific "pendulum swing" like response to a previous low of the plasma vitamin A level has to be considered as a valuable prognostic sign.



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# THE PROTHROMBIN RESPONSE TO LARGE DOSES OF SYNTHETIC VITAMIN K IN LIVER DISEASE\*

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THE liver is a most versatile organ. Its activities include various types of cellular physiology, principally synthesis, storage, conjugation, catabolism and excretion. Although subject to humoral influence, the functions, nevertheless, appear to be devoid of interdependence. However, despite the "dissociation,"<sup>1</sup> certain of the mechanisms exhibit with significant constancy a higher degree of susceptibility to pathologic change than the others. Recently, Drill and Ivy<sup>2</sup> found abnormal retention of bromsulphalein to be the earliest detectable alteration in function following the production of liver damage in dogs by the administration of carbon tetrachloride.

At the time the paper by Drill and Ivy<sup>2</sup> appeared we were engaged in a similar study in both dogs and man. It is desired in this communication to present the results of our experiments.

The purpose of the investigation was to determine the behavior of the prothrombin level in liver disease artificially induced in dogs and occurring clinically in man, and the effect of large doses of synthetic vitamin K in such conditions. The study included serial estimations of the prothrombin time before and after the repeated administration of synthetic vitamin K. In some of the clinical cases and in the dogs the comparative sensitivity of other liver function tests was determined also, especially bromsulphalein retention.

## OBSERVATIONS IN DOGS

Liver damage was produced in dogs by oral administration of 1 c c per kg of a 50 per cent solution of  $\text{CCl}_4$  in oil at intervals of three to four days. Eight dogs were used weighing between 4.5 and 10 kg. The animals were kept on a diet of Purina Checker Dog Food.  $\text{CCl}_4$  was given to all of the dogs on the third, seventh, eleventh and fourteenth days after the initial dose. Injections of synthetic vitamin K (Hykinone)<sup>†</sup> were given to dogs 3, 6, 7, 8 (see table). The animals yielded evidence of liver damage by retention of the dye. The remaining dogs which had suffered degree of injury were used as controls and were not given Hykinone. The dose of Hykinone used was 15 mg per kg on the first two days and 10 mg per kg daily for the remainder of the experiment.

\* Received for publication September 16, 1944.

This is No VIII of the series "Studies in Prothrombin."

<sup>†</sup> Hykinone = Menadione — sodium bisulfite prepared by the Abbott Laboratories.

Determinations of bromsulphalein retention were made before, during, and after the experiment, as shown in the table, by injection of 5 mg per kg of the dye intravenously and determination of retention in the serum 30 minutes after the injection. The retention of less than 10 per cent was con-

TABLE I

Dog No and Weight	Days											Remarks
	1	2	4	6	8	11	12	14	16	19	22	
1 6.9 kg		12 19 10%		11 19 10%		9 20 40%		9.5 18.5 10%		7 22* 10%	9 20 10%	
2 4.54 kg		10.5 17.5 10%		11 21.5 15-20%		8.5 21 45%						Died on 13th day
3 10 kg		11.5 19 10%		10 23 10-15%		9 16.5 10%		11 15 10%		7 15 10%	9 18 10%	Hykinone on 12th until 18th day
4 5 kg	CCl <sub>4</sub> given to all dogs	12.5 21 10%	CCl <sub>4</sub> given to all dogs	12 27 10%	CCl <sub>4</sub> given to all dogs	8.5 20.5 20%	CCl <sub>4</sub> given to all dogs	11 26 30%	CCl <sub>4</sub> given to all dogs	9 23 10%	9.5 22 —	
5 6.37 kg		10.5 17.5 10%		9.5 20 10%		7 17 10%		8.6 20 60%		6.5 17* 10%	9 18 10%	
6 5.45 kg		11 18 10%		18 70 30%		10 35 20%		12.5 42 35%†		7 24* 10%	9.5 21.5 10%	Hykinone on 12th until 18th day
7 5 kg		12 19 10%		11 25 10%		9.5 24 20%		9.5 13.3 10%		7.5 15.5 10%	10 16 20%	Hykinone on 12th until 18th day
8 4.54 kg		11 21 10%		10 31 30%		10.5 40 60%		17.5 67 70%†				Hykinone on 12th and 13th days Died on 14th day

\* Clotted before CaCl<sub>2</sub> added. Results are on cold plasma

† Icteric plasma

The uppermost figure refers to prothrombin time of whole plasma

The middle figure refers to prothrombin time of 12.5 per cent plasma

The lower figure refers to per cent of bromsulphalein retention

CCl<sub>4</sub>—1 c.c./kg. of 50 per cent solution in oil orally

sidered normal. At the same time (or not more than 24 hours later) estimations of the prothrombin time of whole and diluted (12.5 per cent) plasma were made using the single-stage method of Quick.<sup>3</sup> Plasma protein determinations were carried out by the Barbour-Hamilton falling drop method. The results of the dye retention and prothrombin time are given in the attached table. The initial results were obtained before the first administration of CCl<sub>4</sub>.

## ANALYSIS OF RESULTS

Before the administration of  $\text{CCl}_4$ , none of the dogs retained as much as 10 per cent of the dye in 30 minutes following the injection. After two doses of  $\text{CCl}_4$  dogs 2, 6, and 8 revealed increased retention, dog 3 remaining at the border line. Only dog 6 showed prolongation of the prothrombin time of the whole plasma whereas dogs 2, 3, 4, 6, 7, and 8 disclosed respective increases of the diluted (12.5 per cent) plasma prothrombin time. After the third dose of  $\text{CCl}_4$  bromsulphalein retention occurred in all dogs except 3 and 5. The prothrombin time did not show a parallel increase. The undiluted plasma prothrombin time in dog 6 returned to normal and the 12.5 per cent plasma prothrombin time became reduced to normal in dogs 3, 4, and 5. Dogs 2, 6, 7, and 8 showed prolonged prothrombin time. Dog 4 disclosed dye retention but normal prothrombin times, whereas in most of the animals the prothrombin time of the diluted plasma remained increased beyond normal limits although not always directly proportional to the degree of dye retention. It is noteworthy that dogs 6 and 8 showed abnormal retention of bromsulphalein and prolonged prothrombin time of the 12.5 per cent plasma but normal whole plasma prothrombin time. Dog 3 yielded on this day undiluted plasma prothrombin time which was less than those observed during the control periods.

After four  $\text{CCl}_4$  injections, dog 2 had already died. Dog 1 revealed normal dye retention and prothrombin time. (It is possible that this animal vomited the last dose of  $\text{CCl}_4$ .) Dog 3 showed normal dye retention and prothrombin time. This animal showed only a transitory abnormality as revealed by both tests at the time of the third  $\text{CCl}_4$  feeding. Dogs 4, 5, 6, and 8 continued to yield abnormal results both in the degree of dye retention and the prothrombin level. Dog 7, however, had less marked dye retention and prothrombin time prolongation than on the previous date.

Hykinone injections were commenced on the day following the fifth and last dose of  $\text{CCl}_4$ . Four days later dog 8 had succumbed and the surviving animals all showed normal or only very slightly increased retention of dye. The prothrombin times of both whole and diluted (12.5 per cent) plasma became reduced. As noted in the table, spontaneous coagulation of the plasma occurred when the plasma was placed in the constant temperature bath. This took place also in the plasma of dogs 1 and 5, which were not given Hykinone. Because of this phenomenon the prothrombin time had to be estimated using cold plasma and consequently the figures must be accepted with this reservation in mind.

The process appears to have been one of over-compensation in the mechanism of restoration toward normal after the artificially induced prothrombinopenia. A similar condition has been observed in man in the presence of liver disease during recovery from the effects of a small dose of Dicumarol<sup>4</sup>. It has also been noted in multiple myeloma particularly in association with hyperglobulinemia<sup>12</sup>.

In dog 4 the prothrombin time probably continued slightly prolonged. Dog 7 showed recurrence of dye retention 22 days after the initial dose of  $\text{CCl}_4$ . The prothrombin level was normal at the time and explanation for the phenomenon is wanting. Only in dog 6 was significant prothrombinopenia still evident. It is noteworthy that this animal revealed the most pronounced prolongation of the prothrombin time during the course of the experiment. The plasma protein figures and the results of the blood counts were not in any respect consistent with the other experimental findings and consequently are omitted.

Autopsies were performed on dogs 2 and 8 which died 12 and 16 days after the initial dose of  $\text{CCl}_4$ , respectively. The liver of dog 2 showed greatly disturbed architecture, granular degeneration and marked fatty infiltration. Evidences of exudation were also visible. Necrosis was not noted. The kidneys revealed cloudy swelling of the tubules, advanced degeneration of the loops of Henle and diffusely distributed areas of early necrosis. The glomeruli were spared. The heart appeared normal.

Dog 8 showed almost identical changes in the liver and in addition hemorrhage within the parenchyma. The kidneys also presented a similar picture with complete obstruction of the lumen of numerous tubules by granular debris. An occasional area of exudation into Bowman's capsule was seen. A mild degree of cloudy swelling was evident in the heart muscle.

#### COMMENT

The data presented in the tables giving the combined results of the prothrombin times and bromsulphalein retention should be compared with the findings of Drill and Ivy. These workers used the same means to produce liver damage in dogs but employed a crude method for estimation of the prothrombin time and a thromboplastic agent of low potency. They concluded that estimation of the prothrombin time was a less sensitive test of disturbed hepatic function than bromsulphalein retention.

Our findings, based upon the use of a highly sensitive and constantly reproducible method, yielded the fact that at least after the first few doses of  $\text{CCl}_4$ , the prothrombin time, as determined by the single-stage procedure (using 12.5 per cent plasma), is as sensitive an indicator of hepatic disturbance as bromsulphalein retention. It appears that generally a rough proportion between the two tests can be demonstrated although in some animals during the later course of the experiments a dissociation is apt to take place. It is of interest that the extent of bromsulphalein retention obtained in the experiments was not as pronounced and constant as in Drill and Ivy's dogs.

After the  $\text{CCl}_4$  was withdrawn both tests revealed restoration to normal except dog 6 in which slight prothrombinopenia continued. Increased retention of bromsulphalein 22 days after the initial dose of  $\text{CCl}_4$  in dog 7 is without explanation.

The rate of recovery from liver damage was uninfluenced in the four dogs in which Hykinone was administered. This has been noted by others<sup>5</sup>. Hypercoagulability, probably due to over-compensation, was observed irrespective of the use of synthetic vitamin K, during the recovery periods.

These experiments reveal the fact that estimation of the diluted (12.5 per cent) plasma prothrombin time is an important and reliable indicator of early liver damage. The method demands the use of a highly potent standardized thromboplastic agent and carefully controlled technique.

It should be borne in mind that liver damage artificially produced by  $\text{CCl}_4$  is not necessarily a true reproduction of the hepatic disorders seen in man. It appears that in man certain forms especially the more acute varieties are, as far as is known, reversible after the toxic agents are withdrawn as was the case in some of the dogs. However, their responses to liver function tests are apt to vary in certain respects from those observed in the dogs, indicating, in such instances at least, that the pathological processes are not identical. This will be illustrated in the data presented below.

#### OBSERVATIONS IN MAN

Prothrombinopenia has been found by others in only 53 per cent of cases of liver disease<sup>6</sup>. There is reason to question this figure because of the comparatively low sensitivity of the method used for estimation of the prothrombin time. Accordingly, we undertook a study of the diluted (12.5 per cent) plasma prothrombin time in a series of cases of liver disease. The investigation was extended to include observations on the response to synthetic vitamin K (Hykinone) in large doses in two groups of cases of liver disease: those with normal prothrombin levels and those with prothrombinopenia.

Twenty-three cases constitute the series, including 18 of Laennec's type of cirrhosis of the liver, two of hemachromatosis (diagnosis confirmed subsequently at autopsy), and one of each of the following: acute arsenical hepatitis (examined during the active stage and later when recovery had occurred), metastatic neoplasm of the liver, and macrocytic (pernicious) anemia in a state of remission following liver therapy.

Details of the particular method used for estimation of the prothrombin time have been presented in previous communications<sup>7,8</sup>. It utilizes the principle of determining prothrombin time in diluted (12.5 per cent) plasma, a procedure shown to be more sensitive than that in which whole plasma alone is used<sup>9</sup>. A standardized thromboplastic agent of high potency is essential for the procedure.

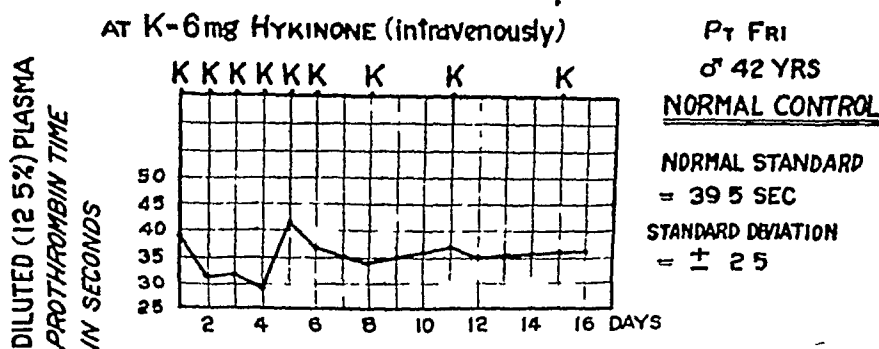
#### DATA

The normal standard diluted (12.5 per cent) plasma prothrombin time was 39.5 seconds (Standard deviation = 2.5). The variations were within the range of 37–44 seconds. All estimations were done in duplicate.

Serial estimations were made on at least five days during a period of one week to establish the existing level of prothrombin. Synthetic vitamin K (Hykinone) was administered parenterally in dosages of 6 mg to 20 mg per day.

For purposes of control six normal subjects were given the identical treatment.

The results in the normals were as follows. The prothrombin time during the first week when no medication was given showed all figures to be within the normal range. Following the administration of Hykinone the prothrombin time became reduced to 36 or 35 seconds for one or two days when it increased to within the normal range, continuing at this level for the duration of the period of observation. One case revealed initially a fall to 29 seconds after which it became elevated to within normal limits (chart 1). One case revealed a sharp rise to 47 seconds for one day from a low figure of 36, following which all of the results continued within the normal range.



The cases of liver disease during the control period before menadione was given revealed a remarkable constancy of the level of prothrombin. Of the 23 cases investigated the resting level of prothrombin was normal in only three instances. Twenty disclosed moderate\* or marked\* prolongation of the prothrombin time. After Hykinone was administered parenterally the cases with established prothrombinopenia showed response patterns as follows: (A) An initial reduction of prothrombin time toward normal for one to three days when it became prolonged to a level in excess of the original figure, followed by a fall to approximately, or slightly below the preëxisting level (chart 2), (B) The prothrombin time remained at about the original level for two or three days when it became increased for two or three days and gradually receded to or slightly less than the original figure (chart 3), (C) Where the resting level of prothrombin was normal, after the third or fourth day of menadione medication the prothrombin time increased slightly at which figure it remained for a few days when it returned to normal again (chart 4).

\* Moderate = between  $1\frac{1}{2}$  and twice normal<sup>4</sup>  
Marked = approximately twice normal

A-STARTED HYKINONE 6mg DAILY (IV)  
B-DISCONTINUED ALL MEDICATION

Pt L & B  
♀ 36 Yrs

DIAGNOSIS -  
CIRRHOSIS OF  
THE LIVER

NORMAL STANDARD  
= 39.5 SEC

STANDARD DEVIATION  
=  $\pm 2.5$

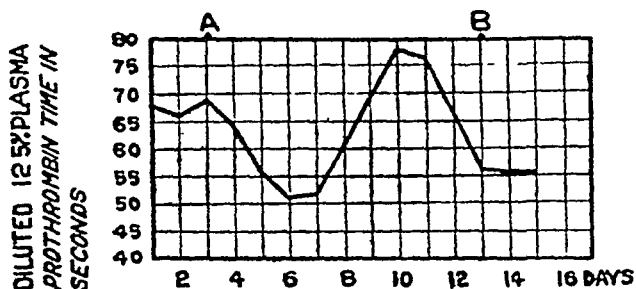
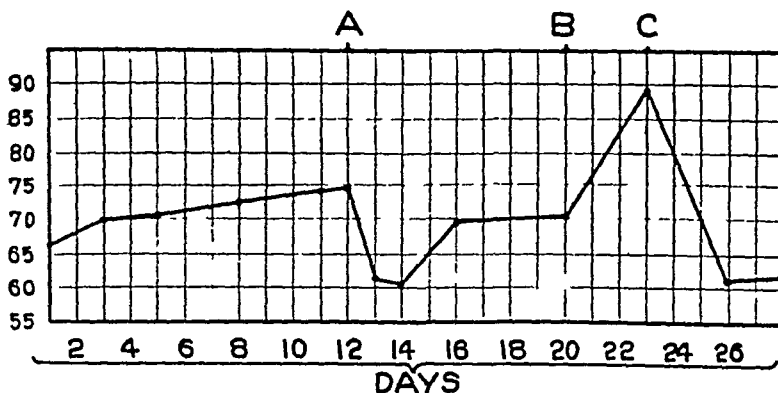


CHART 2

AT A - STARTED HYKINONE 6mg DAILY (intraven)  
AT B - INCREASED to 12mg  
AT C - MEDICATION DISCONTINUED

Pt Gin. ♂ 52 yrs  
DIAGNOSIS  
LAENNEC'S  
CIRRHOSIS  
OF THE LIVER

DILUTED PLASMA (12.5%)  
PROTHROMBIN TIME  
IN SECONDS



NORMAL STANDARD 39.5 — STANDARD DEVIATION - 2.5

CHART 3

AT A - STARTED HYKINONE 12mg DAILY (IV)  
AT B - INCREASED to 20mg  
AT C - ALL MEDICATION DISCONTINUED

Pt BL Age 42♀  
DIAGNOSIS  
Liver Disease  
Cirrhosis?

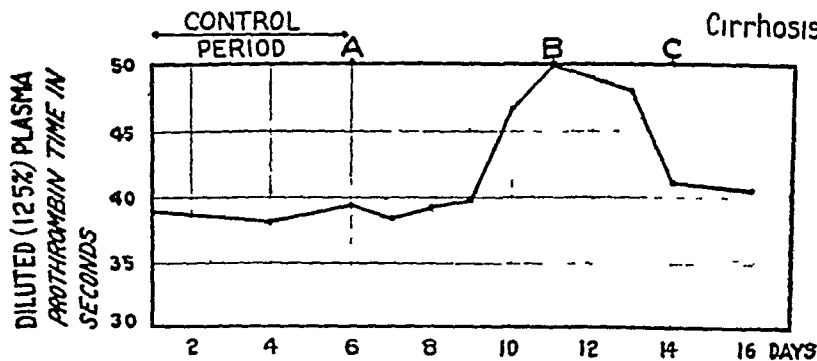


CHART 4



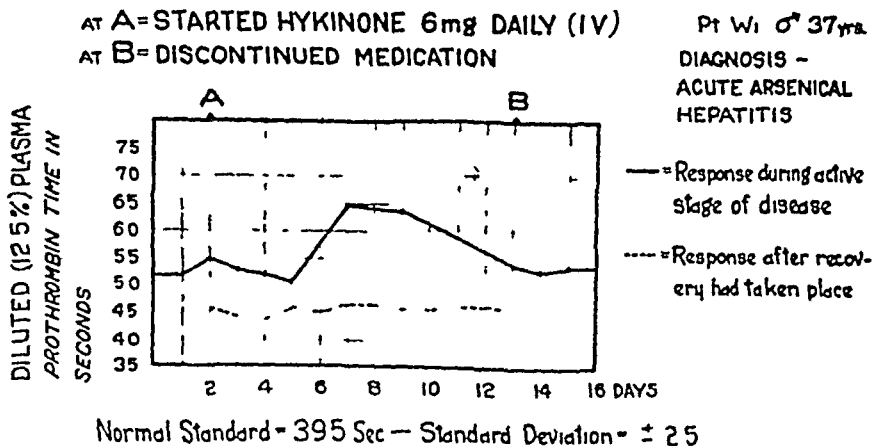


CHART 5

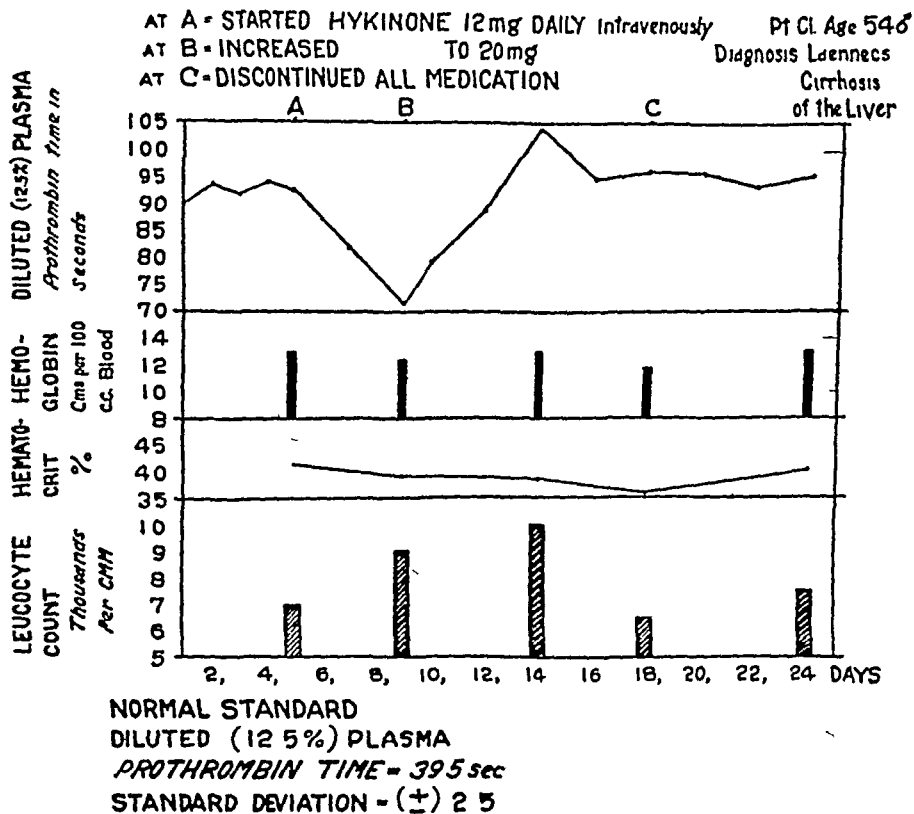


CHART 6

Attempt was not made in every case to compare the findings with other liver function tests. We attempted primarily to determine the prothrombin time in the presence of liver damage. It is worthy of especial note, however, that in four instances (i.e., the three cases in which the prothrombin levels were normal and one case of hemochromatosis and refractory anemia which

on section showed fatty degeneration of the liver lobules) deviation of the prothrombin curves from the normal after Hykinone was in each case the only abnormality in liver function detected clinically. The bromsulphalein retention was not abnormal in any of these four cases, and only one revealed abnormal cephalin flocculation.

### ANALYSIS OF RESULTS

The data herein described indicate that under the conditions presented the system for elaborating prothrombin functions at a constant and apparently maximum level. In the presence of normal function additional stimulation by vitamin K serves to augment the activity. This continues for only a short transitory interval after which the tempo of prothrombin elaboration returns to the normal initial rate despite the continued administration of menadione. In the presence of liver damage with existing normal prothrombin levels, the persistent stimulation induced by repeated parenteral administration of synthetic vitamin K appears temporarily and partially to exhaust the prothrombin system for a few days when it recovers its normal rate and continues at this level.

Where prothrombinopenia had already been established in liver disease, the response to large doses of antihemorrhagic substance reveals an inability to revert to normal. This has previously been reported by earlier observers<sup>10</sup>. The tendency toward temporary and partial exhaustion of the prothrombin mechanism was decidedly more pronounced in such cases than in those with normal initial prothrombin levels. An analysis of data presented by previous authors has revealed comparable responses, although the phenomena seem to have attracted no especial interest<sup>11, 13</sup>.

It is noteworthy that the case of acute arsenical hepatitis yielded the reaction of liver damage during the active stage and showed a normal response after recovery had taken place (chart 5).

Emphasis is placed upon the findings in four cases in which other procedures including bromsulphalein retention were normal and in which pathologic prothrombin curves constituted the only laboratory demonstration of liver disease.

Initial prothrombinopenia was found in 20 of our series of 23 cases of liver disease.

### DISCUSSION

We find, as have previous authors,<sup>3, 10, 11, 13</sup> that in the presence of liver disease an established prothrombinopenia cannot be restored to normal by the administration of synthetic vitamin K. Such a sequence of changes portends liver disturbance (unless other explanations are discovered).

The sensitivity of the prothrombin estimations is markedly increased by the use of diluted (12.5 per cent) plasma. It accounts for our finding pro-

thrombinopenia in a much higher proportion of cases than others using whole plasma †

The following procedure is suggested as a means of establishing the presence of hepato-cellular pathology the resting level of diluted (12.5 per cent) plasma prothrombin time is determined. Synthetic vitamin K is given parenterally daily for about one week. If prothrombinopenia is present and it fails of correction after menadione, liver disease is presumed to be responsible. Restoration to a normal prothrombin level indicates adequate hepatic function. Where the resting prothrombin time is normal and it becomes prolonged after several administrations of menadione (the increased prothrombin time lasts for two or three days) hepatic disturbance should be considered the cause, unless other reasons are revealed. We have observed it in man only in the presence of liver damage.

On the question of the relative sensitivity of the various liver function tests, the data herein presented indicate that the estimation of the diluted (12.5 per cent) plasma prothrombin time and the response to parenteral menadione is no less sensitive than bromsulphalein retention. Actually, in four cases of liver disease we found the prothrombin curves to be superior to bromsulphalein retention or cephalin flocculation in revealing hepatic damage.

By virtue of its chemical constitution menadione is apt to cause hemolytic anemia. In other series of experiments to be published separately we shall describe the effects in animals of doses many times in excess of those administered in our investigations in man. The findings indicate that after huge doses there can be produced regularly an anemia characterized by a fall in hemoglobin and erythrocytes and occasionally the appearance of normoblasts in the circulating blood. Upon withdrawal of the quinone there follows a prompt return to a normal blood picture. In the above experiments in man we noted anemia only rarely and when it did arise it was always mild, and in every case a return to the normal blood picture occurred promptly after the withdrawal of the Hykinone (chart 6).

### SUMMARY

In dogs, following the administration of  $\text{CCl}_4$ , the prothrombin time of diluted (12.5 per cent) plasma was found to be as sensitive an indicator of hepatic disturbance as bromsulphalein retention.

Generally a rough correlation between the two tests was demonstrated. Later in the course of the experiments a dissociation of the procedures occurred.

The rate of recovery following the withdrawal of  $\text{CCl}_4$  was uninfluenced by the administration of synthetic vitamin K.

In man, prothrombinopenia as determined by estimation of the diluted

\* Advanced renal disease, especially with azotemia, appears to augment the prothrombin level. (Possibly prothrombin is eliminated by the kidneys.)

(12.5 per cent) plasma prothrombin time was demonstrated in 20 out of 23 cases

Following repeated parenteral administration of 6 to 20 mg of Hykinone almost daily, characteristic curves of the prothrombin response were observed in normals and in cases of liver disease both with preexisting prothrombinopenia and with normal resting levels of prothrombin

Deviations from the normal in response to synthetic vitamin K were found to occur in instances of liver disease where bromsulphalein retention and cephalin flocculation were normal

The findings were obtained by the estimation of diluted (12.5 per cent) plasma prothrombin time

Repeated administration of large doses of menadione was found to cause anemia which returned to normal promptly upon withdrawal of the anti-hemorrhagic substance

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# LIVER DYSFUNCTION HYPERGLYCEMIA: ITS ETIOLOGY AND RELATION TO DIABETES MELLITUS \*

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RECENT work has shown that numerous conditions other than diabetes mellitus are accompanied by hyperglycemia, the more significant of these conditions include obesity, liver damage, and hyperpituitarism. That this symptom appears in such diverse diseases is explicable by the fact that control of the blood sugar is determined not only by the level of insulin in the blood but by the state of the liver, kidneys and gastrointestinal tract as well as by the level of the pituitary-adrenal hormones

## OBSERVATIONS

While engaged in testing a modified insulin preparation in a series of diabetic patients, the authors felt obliged to ascertain directly the severity and definiteness of the disease in each case. This was done by keeping the patient on his regular hospital diet but withholding insulin for 24 to 48 hours. Blood sugars were run at regular intervals (four to eight hours) and urine samples were checked for sugar and acetone every four hours. At the end of the experimental period the patients were brought back under control with suitable doses of regular insulin.

This work brought to our attention very forcefully the considerable differences between the two major classes of diabetes mellitus patients: the adult and juvenile diabetics. The results obtained in two representative cases are shown in table 1. Differences just as marked are noted when (a) the onset and course and (b) the response to treatment of these two types of diabetics are considered. These may be summarized as follows:

(a) *Onset and course* Juvenile diabetics (i.e., patients suffering from insulin deficiency) are generally first observed in a very acidotic or pre-comatose condition. Characteristically, they give a history of polyuria and polydipsia for about a month with polyphagia and weight loss for an even longer time. When the patient has marked complaints, sugar and acetone are always found in the urine and an acidosis, hypercholesterolemia, hyperglycemia and dehydration are not infrequent. Unless treated by insulin they progress rapidly to coma and death. But given an adequate diet and insulin, they soon show excellent clinical condition.

On the other hand, most "adult diabetics" (hepatic dysfunction hyperglycemics) show no such extreme course, but are generally picked up on a

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routine examination of the urine which very often shows sugar but rarely acetone. Polyuria, polydipsia, polyphagia, and weight loss are only sporadically found. The chief findings are glycosuria, hyperglycemia and certain changes in the blood picture characteristic of low grade liver damage. The onset of the disturbance is late in life and it frequently involves obese individuals. The authors, among others, have found that lack of insulin treatment gives no increase in the symptoms over a long period of time. Many of these cases show spontaneous remission of the glycosuria for no apparent cause<sup>1, 2, 8</sup>

TABLE I  
Effect of Withholding Insulin from Adult and Juvenile Diabetics

Hours	Case 1			Case 2		
	Blood Sugar mg %	Urine		Blood Sugar mg %	Urine	
		Sugar	Acetone		Sugar	Acetone
0	111	0	0	218	+	0
4	119	0	0	243	+	0
8	164	0	0	269	++	0
12	292	+++	0	261	+++	0
16	344	++++	0	248	+++	0
20	395	++++	0	227	++	0
24	419	++++	0	213	++	0
28	442	++++	0	—	+	0
32	—	++++	0	274	++	0
36	438	++++	0	—	+++	0
40	—	++++	0	251	+++	0
44	450	++++	+	—	+++	0
48				208	+	0

*Case 1* A white male, 32 years old, who had been a diabetic for 20 years. He was controlled on 65 units of protamine zinc insulin and 15 units of regular insulin administered together every morning.

*Case 2* A white male, 56 years old, who had been diagnosed as diabetic six years previously. He was given a morning dose of 15 units of regular insulin daily.

Both patients were maintained on a normal hospital régime during the experiment. Zero time in the table represents 7 00 a m, the usual hour for the daily insulin injection. During the experiment no insulin was administered, the last dose having been given 24 hours before zero time. Feedings were at 7 30 a m, 11 30 a m, and 5 00 p m, with a snack at 9 00 p m before retiring. Lunch was the largest meal of the day.

(b) *Treatment* The juvenile type has a moderate to high insulin requirement, shows a good response to protamine zinc insulin, and gets along well on a moderate carbohydrate diet (180–350 C, 100 P, 60 F). The "adult type" requires only low to moderate insulin dosages and, in general, is quite sensitive to regular insulin but responds poorly to protamine zinc insulin. We have found that these hyperglycemic adults show greater improvement on a high to very high carbohydrate diet than when one low to moderate in carbohydrate is prescribed<sup>1, 8</sup>

These differences are so considerable that we were forced to the conclusion that a fundamental difference existed between these two types of diabetics and that rather than suffering from variants of the same disease, two different diseases showing similar symptoms were existing side by side.

The following facts led us to take the stand that the large majority of adult hyperglycemics, that is, individuals developing hyperglycemia after the third decade, were suffering from low grade liver damage rather than the insulin deficiency implied in a diagnosis of diabetes mellitus

(a) The liver is the organ responsible for regulating the blood sugar

(b) Disturbances of liver function would be expected to cause alterations in the carbohydrate regulation of a certain number of cases and, indeed, this has already been shown to be the case by other investigators <sup>4, 5, 6, 7, 8, 9, 10</sup>

(c) Adult diabetics are almost exclusively people in the fourth decade or older, a time when low grade liver dysfunction would be much more prone to appear than in younger people

(d) In the patients we observed many of the adult diabetics had a history of excessive alcoholism and poor diet

(e) Most important, all cases of adult diabetics which we rediagnosed as liver dysfunction hyperglycemics showed evidences in their blood chemistry of subclinical or low grade liver disease

Consequently, our treatment of these individuals was altered. In many instances, these cases were treated as pure liver disease patients, insulin being withheld and therapy consisting of a high carbohydrate, high protein and low fat diet. These people have in the great majority of cases shown a pronounced improvement in their "diabetic" symptoms. In the cases where no concomitant insulin deficiency existed (this group includes about 80 per cent of the adult "diabetics" in our experience) there was never in any case an increase in the extent of the hyperglycemia or a more marked impairment of the glucose tolerance even though no insulin was administered. Although the proportion of "adult diabetics" with pure liver disease is large, there still are many who possess either a relative or an actual insulin deficiency together with their liver disease. This may be due to degenerative changes in the pancreas or to associated disease in the other endocrine systems. However, these deficiencies are generally mild, and the patients are best treated with small dosages of insulin and high carbohydrate diets <sup>2, 3, 11</sup>

As a result of daily experience, we have taken the stand that in those adults whose hyperglycemia becomes manifest late in life (after the third or fourth decade), management should be directed against the primary disease, usually liver damage, and not against the symptom, hyperglycemia. The physician is then faced with the problem of determining whether he is dealing with a case of pure liver damage, pure diabetes or a mixture of both liver disease and insulin deficiency. This is a difficult problem, especially since as has been emphasized above, the majority of "adult diabetics" are only subclinical liver disease patients and as such are not easily recognized. However, these obstacles can be partly minimized by the use of certain simple and readily available laboratory tests

The following procedure has been found most satisfactory (1) A complete series of blood chemical tests should be made to discover if any deviations characteristic of liver deficiency exist. This should include determina-

tion of total protein, albumin-globulin (A/G) ratio, non-protein nitrogen (N P N ), uric acid, cholesterol and cholesterol esters, and one of the serum precipitation tests (Takata-Ara, colloidal gold, etc ) (2) Some of the standard dye elimination tests and hippuric acid synthesis, etc (3) The intravenous glucose-tolerance test As Soskin has demonstrated, many liver cases give an intermediate curve between normal and the severely diabetic<sup>10</sup> If this is found, it is significant, but we have on record a number of unquestioned cases of liver disease who give a very severe diabetic type of response It should be remembered that in liver disease, all liver functions including the ability to regulate the blood glucose may sustain any degree of impairment from mild to severe The use of any one test alone gives anomalous results and makes accurate diagnosis of liver dysfunction impossible

Other diagnostic criteria are found in the history and the character of response to therapy As emphasized in the early part of this paper, one should be most reluctant to make a diagnosis of diabetes mellitus in an elderly individual who does not give the typical onset and course of juvenile diabetes and who has a history of inadequate diet or repeated exposure to such hepato-toxic agents as alcohol, or both The response to various types of insulin control is significant A high sensitivity to regular insulin with a poor response to protamine zinc insulin is characteristic of the cases of liver disease These respond excellently to a high carbohydrate diet without insulin They spill no more sugar on a high than on a low carbohydrate diet, and their blood sugars are not significantly increased by the high carbohydrate therapy Of major importance is the response of the patient to high carbohydrate, no insulin therapy, the maintenance of an excellent clinical condition and the improvement thereof over a fair period of time indicate unequivocally the absence of actual insulin deficiency These observations, correlated with the previous laboratory tests, will make possible the correct evaluation of the patient's status

Similar conclusions have been reached by Newburgh in his work on "obese diabetics"<sup>2</sup> He observed the same symptomatology which we had noted in our "adult diabetics" and found that the most important therapy in these cases was reduction of the individual's weight In most cases a lessening of the individual's obesity was accompanied by a marked increase in his glucose tolerance Newburgh's conclusion was that although the cause of the disturbance in these individuals is obscure, they are not suffering from diabetes Boyd<sup>12</sup> has suggested that the difficulty in these cases may be caused by an infiltration of the liver with fat In these cases where the caloric intake must be kept low, we merely adjust the diet to give the patient a high carbohydrate-fat ratio, provided there is no acidosis

The patient who displays evidence of liver damage and a moderately good response to protamine zinc insulin may be considered as having an associated mild insulin deficiency, and may be treated with a high carbohydrate diet and moderate insulin dosage However, in no such case should the emphasis be placed upon the maintenance of a sugar-free urine, one should stress,



rather, the treatment of the liver condition. The major criterion of the treatment should be the patient's clinical status.

The scheme of diagnosis and treatment outlined above is not merely theoretical. Its clinical application has met with considerable success for over a year in our work at Cook County Hospital. This is shown in the cases detailed below.

#### CASE REPORTS

*Case 1* D G, a white male, aged 50 years, came to the hospital with complaints of extreme progressive fatigue for the preceding three years and of diabetes mellitus for the preceding 10 years. This patient had never taken insulin, but was on a strict, low carbohydrate diet. Physical examination revealed the presence of a double mitral murmur, but no other abnormalities, and no evidence of cardiac decompensation. The hematologic picture was within normal limits. Urinalysis revealed a 4 plus test for sugar, negative test for acetone, albumin, and was negative microscopically. The specific gravity of the urine was 1.020. Blood chemistry: Total proteins, 6.6 gm per cent, albumin, 3.6 gm per cent, globulin, 3 gm per cent, uric acid, 9 mg per cent, cholesterol, 200 mg per cent, cholesterol esters, 68 per cent, creatinine, 2 mg per cent, non-protein nitrogen, 48 mg per cent. The fasting blood sugar varied on successive days from 110 to 290 mg per cent. The Exton-Rose glucose tolerance test, after a three day high carbohydrate diet, was: fasting, 290 mg per cent,  $\frac{1}{2}$  hr, 270 mg per cent, 1 hr, 250 mg per cent. An intravenous glucose tolerance test was: fasting, 110 mg per cent,  $\frac{1}{2}$  hr, 220 mg per cent, 1 hr, 220 mg per cent, 2 hr, 100 mg per cent. The patient's complaint was diagnosed as liver dysfunction hyperglycemia and he was placed on a diet of carbohydrate, 450 grams, protein, 110 grams, fat, 65 grams. He was also given vitamin B complex and choline chloride, two grams per day. Fatigue disappeared soon after the onset of therapy and the patient became more active in his business than he had been in the past 10 years. His subjective condition was excellent. After 14 months of therapy, the total proteins were 6.2 gm per cent, albumin, 4.2 gm per cent, globulin, 2.6 gm per cent. There was no more glycosuria. The intravenous glucose tolerance was essentially unchanged.

*Case 2* G L, a white male, aged 55, came into the hospital complaining of uncontrolled diabetes and a sensation of weakness. The patient had been diagnosed as a diabetic 10 years previously and placed on a low carbohydrate, high fat diet without insulin. At that time he was very obese, weighing 270 pounds. He also gave a history of excess alcoholism of many years' duration. During the intervening 10 years the patient continued drinking, although more moderately. Physical examination revealed slightly icteric sclerae and an irregularly nodular liver, palpable three fingers below the costal margin. The essential findings in the urine were a 4 plus test for sugar and an occasional trace to one plus test for acetone. Hematologic picture was normal. Blood chemistry: total proteins, 5.8 gm per cent, albumin, 2.3 gm per cent, globulin, 3.5 gm per cent, non-protein nitrogen, 46 mg per cent, icterus index, 14, total cholesterol, 150, Takata-Ara test, 4 plus. An intravenous glucose tolerance test, after three days on a high carbohydrate diet, was: Fasting, 350 mg per cent,  $\frac{1}{2}$  hr, 430 mg per cent, 1 hr, 397 mg per cent, 2 hr, 340 mg per cent, 3 hr, 326 mg per cent. A diagnosis of liver dysfunction hyperglycemia was made. The diet ordered was: carbohydrate, 450 grams, protein, 110 grams, fat, 60 grams. He was also given vitamin B complex and choline chloride, two grams daily. Marked subjective improvement occurred rapidly, and no acetone could be found in any urine sample. Eight months later the total proteins were 6.0 gm per cent, albumin, 3 gm per cent, globulin, 3 gm per cent. The urine showed a two plus test for sugar, no acetone. Icterus index was 4.

*Case 3* S T, a white male, aged 40, was admitted to the hospital in coma, with an admission diagnosis of diabetic coma. Physical examination revealed a hard, nodular liver, palpable four fingers below the costal margin, and a moderate papilledema. The catheterized urine sample was 4 plus for sugar and negative for acetone. A history was obtained from his wife. Six months previously this patient had been diagnosed as having diabetes mellitus and was placed on a diabetic diet without insulin. He had continued uneventfully until one day before admission, when he collapsed at work. A physician had administered 180 units of regular insulin prior to admission. Further questioning revealed that the patient had been a heavy alcoholic for the past 20 years. A diagnosis was made of severe portal cirrhosis with cerebral edema. The therapy instituted was continuous infusion of 10 per cent glucose in saline. The temperature gradually rose, and 24 hours after admission the patient died. Blood chemistry reports showed a  $\text{CO}_2$  combining power of 44 volumes per cent, total proteins were 60 gm per cent, albumin, 21 gm per cent, globulin, 49 gm per cent. Blood sugar on admission was 194 mg per cent. The urine at no time showed more than traces of acetone. Autopsy showed hemachromatosis of the liver and pancreas, severe portal cirrhosis of the liver, and acute focal necrosis within the liver. The pathologist's opinion was that the cause of death was the acute focal necrosis of the liver.

*Case 4* J S, a white male, age 65, was admitted to the hospital with a diagnosis of arteriosclerotic heart disease and diabetes mellitus. Physical examination revealed left heart enlargement, the left heart border was in the left axillary line in the sixth interspace. There was a harsh systolic murmur at the apex and parasternal border. The liver was palpable, and non-tender. An electrocardiogram showed evidence of left axis deviation and coronary sclerosis. The blood pressure was 195 mm Hg systolic and 110 mm diastolic. The urine was negative except for a 4 plus test for sugar. This patient had been on a dosage of protamine zinc insulin, 20 units daily for the past five years, since the date of onset of his diabetes. The patient complained of many attacks of chest pain coincidentally with insulin reactions. Blood chemistry: total proteins, 50 gm per cent, albumin, 24 gm per cent, globulin, 26 gm per cent, non-protein nitrogen, 40 mg per cent. Diagnosis: Hypertensive heart disease and liver damage. Therapy was a diet of carbohydrate 350 grams, protein 100 grams, and fat 60 grams. No insulin. Vitamin B complex was administered. Glucose tolerance test (Exton-Rose) on admission was: fasting, 177 mg per cent,  $\frac{1}{2}$  hr, 249 mg per cent, 1 hr, 220 mg per cent. Eight months later the fasting blood sugars varied from between 100 mg per cent to 150 mg per cent, and there had been marked subjective improvement over those months. No change in the plasma proteins was observed.

*Case 5* H K, a white male, aged 85 years, was admitted to the hospital with a diagnosis of decompensated arteriosclerotic heart disease and diabetes mellitus. In the history, it was noted that the patient had been diabetic for the past 35 years and had been taking 20 units of insulin daily for the past 18 years. The patient was digitalized and rapidly compensated. Insulin was stopped. Fasting blood sugars varied from 162 to 204 mg per cent. The total proteins were 51 gm per cent, albumin, 24 gm per cent, globulin, 27 gm per cent, non-protein nitrogen, 45 mg per cent. Urinalysis showed a 4 plus test for sugar and was negative for acetone. The treatment instituted was a diet of carbohydrate, 350 grams, protein, 80 grams, fat, 55 grams. Vitamin B complex was given, but no insulin. Thirteen months after admission his condition was good. No essential changes in the blood sugar or plasma proteins had occurred. There was never any acidosis.

*Case 6* J T, white male, aged 54, came into the hospital for investigation of his "diabetes," which had just been discovered on routine analysis by a physician treating a "sore on the toe." This patient felt well and had come in only because the

physician told him his diabetes should be investigated. Physical examination was essentially negative. Blood chemistry was within normal limits except for plasma proteins: total proteins, 6.8 gm per cent, albumin, 3.2 gm per cent, globulin, 3.6 gm per cent. An intravenous glucose tolerance test was: fasting, 172 mg per cent,  $\frac{1}{2}$  hr, 230 mg per cent, 1 hr, 220 mg per cent, 2 hr, 175 mg per cent, 3 hr, 169 mg per cent. Diagnosis was made of liver dysfunction hyperglycemia. Therapy consisted of a diet of carbohydrate, 475 grams, protein, 110 grams, fat, 70 grams. Vitamin B complex and choline chloride, two grams daily, were given. The patient felt well on this régime. Ten months later fasting blood sugars varied from 70 mg per cent to 182 mg per cent. There were no essential changes in the protein values.

*Case 7* L M, white male, aged 51, was found to have sugar in the urine and was referred for study. There were no subjective complaints. Physical examination was essentially negative. Blood chemistry was: total proteins, 7.0 gm per cent, albumin, 4.0 gm per cent, globulin, 3 gm per cent, non-protein nitrogen, 38 mg per cent, total cholesterol, 175 mg per cent, esters, 60 per cent, Takata-Ara two plus. The fasting blood sugar was 205 mg per cent. An intravenous glucose tolerance test showed: Fasting, 187 mg per cent,  $\frac{1}{2}$  hr, 234 mg per cent, 1 hr, 209 mg per cent, 2 hr, 195 mg per cent, 3 hr, 201 mg per cent. Diagnosis of liver dysfunction hyperglycemia was made. Treatment ordered was a diet of carbohydrate, 475 grams, protein, 100 grams, fat, 65 grams, vitamin B complex was also given. This patient was watched for nine months, at the end of which time he was still feeling fine and was without subjective complaints. Fasting blood sugars varied from 120 mg per cent to 173 mg per cent. Glycosuria was minimal.

*Case 8* J R, colored male, 57 years of age, was admitted to the hospital because of uncontrolled diabetes mellitus. This patient gave a history of having had diabetes mellitus for two years. He was on a diet and 25 units of protamine zinc insulin per day, but on this regime the patient would have reactions in the late afternoon, and would still find sugar in his urine in the mornings. Physical examination revealed a palpable liver but was otherwise negative. Blood chemistry: total proteins, 5.2 gm per cent, albumin, 3.3 gm per cent, globulin, 1.9 gm per cent, non-protein nitrogen, 30 mg per cent, cholesterol, 150 mg per cent. The cephalin flocculation test was two plus. Intravenous glucose tolerance test, after three day preparation with high carbohydrate diet and no insulin: fasting, 155 mg per cent,  $\frac{1}{2}$  hr, 208 mg per cent, 1 hr, 200 mg per cent, 2 hr, 183 mg per cent. Urinalysis showed a 4 plus test for sugar, but negative tests for acetone. A therapeutic diet of carbohydrate, 400 grams, protein, 100 grams, fat, 60 grams was ordered. Vitamin B complex was also ordered. All insulin was discontinued. The patient felt very well, and very much appreciated the absence of insulin reactions. Six months after the onset of therapy, the total proteins were 6.1 gm per cent, albumin, 4 gm per cent, globulin, 2.1 gm per cent, cholesterol was 165 mg per cent. The blood sugars and glucose tolerance tests were essentially unchanged. There was no increase in the glycosuria and there was never any acetone in the urine.

*Case 9* S S, aged 64, white male, came into the hospital with complaints of dizziness and weakness for six months, and of diabetes mellitus for nine years. Physical examination revealed a blood pressure of 240 mm Hg systolic and 120 mm diastolic, a markedly enlarged left heart, to the anterior axillary border in the seventh interspace, a rough harsh systolic murmur at the apex, and a grade four hypertensive neuroretinopathy in the fundi. There were many coarse rales throughout the lungs. The urine showed heavy albumin, red cells, casts, and sugar. The specific gravity varied between 1.010 and 1.015. The non-protein nitrogen was 110 mg per cent, total proteins, 4.0 gm per cent, albumin, 2.2 gm per cent, globulin, 1.8 gm per cent. The blood sugars varied from 130 mg per cent to 247 mg per cent. The patient had previously been on an insulin dosage of 40 units of regular insulin daily. This was

stopped, and intravenous glucose and fluids were given. The blood sugars fell to fasting levels of 111 mg per cent to 137 mg per cent. At no time was there acetone in the urine. After two months, the patient succumbed in uremic coma. There were never any signs of a diabetic type of ketosis.

*Case 10* K. T., a white male, aged 48, came into the hospital with uncontrolled diabetes and bilateral inguinal hernia. Surgery was requested. This patient had been diagnosed as a diabetic 12 years previously, and had been placed on a low carbohydrate diet and given 40 units of protamine zinc insulin daily. Urinalysis, on admission, showed sugar, 4 plus, acetone, 4 plus, albumin and microscopic negative. Blood count was negative. Admission blood sugar was 365 mg per cent. Total proteins were 4.3 gm per cent, albumin, 1.9 gm per cent, globulin, 2.4 gm per cent, non-protein nitrogen 45 mg per cent, total cholesterol 279 mg per cent, esters 56 per cent. Physical examination was negative except for the presence of the bilateral inguinal herniae. The patient was originally given a diet of carbohydrate, 120 grams, protein, 60 grams, and fat, 70 grams. Thirty units of regular insulin were injected three times a day, before meals. On this regime, hyperglycemia, acidosis and weight loss continued unabated. At this point the authors were called in. A diagnosis was made of diabetes mellitus with associated liver damage. The diet was changed to carbohydrate, 400 grams, protein, 110 grams, fat, 70 grams. Vitamin B complex was given. Regular insulin, units 25, t i d, a c, and 15 units of regular insulin at bed-time with 10 ounces of orange juice were ordered. The blood sugars fasting and after meals dropped to normal, the acidosis disappeared. The patient gained weight and marked subjective improvement occurred. The insulin was then changed to protamine zinc insulin, units 60, and regular insulin, units 30, every morning in different sites. Fasting blood sugars ranged from 90–115 mg per cent. The total proteins rose to 6.2 gm per cent, albumin, 3.4 gm per cent, globulin 2.6 gm per cent. Patient was ready for surgery. The operation was performed and the patient had an uneventful recovery.

## DISCUSSION

Hyperglycemia and glycosuria have long been recognized as findings in such conditions as head injuries, the pneumonias, severe toxemias, and chromaffin tissue tumors. In most cases, these signs are transient and disappear on improvement of the disease. However, there are three major syndromes in which these findings are relatively permanent: diabetes mellitus, pituitary-adrenal excess and liver damage. Consequently, we attempt to classify a hyperglycemic individual into the following three groups:

(1) *Actual insulin deficiency* This is due to malfunction of the islets of Langerhans in the pancreas. Here, insulin must be given. Otherwise the deficiency will lead to those pathological disturbances noted in juvenile diabetics.

(2) *Relative insulin deficiency* This is due primarily to an excessive production of those hormones of the pituitary and adrenals which regulate carbohydrate metabolism. Since these hormones operate mainly as a counter-balance to insulin, their relative excess causes hyperglycemia and increased gluconeogenesis with ketosis. This results in a clinical picture which resembles the earlier stages of a true diabetes mellitus.

Administration of insulin corrects this imbalance and results in the disappearance of the "diabetic" symptoms. However, there is no actual insulin

deficiency, and even if exogenous insulin is not administered, these patients show no severe symptoms, coma or death

(3) *Hepatic insufficiency* This has as one of its most frequent manifestations an inability properly to regulate the blood sugar. We have found that a majority of the adult "insulin-insensitive" diabetics are not true diabetics at all but are cases of liver injury showing hyperglycemia as one of the indications of their hepatic dysfunction. The outstanding findings in these individuals are

- a a vacillating blood sugar level, generally higher than normal, running on the average about 200 to 250 mg per cent,
- b a diabetic or semidiabetic glucose tolerance curve,
- c a normal blood level of acetone bodies in well nourished patients,
- d alterations in the blood values of uric acid, non-protein nitrogen, total protein, A/G ratio, cholesterol and cholesterol esters, and bilirubin \*

The authors offer the following explanation for these findings. All functions of the liver are mediated by enzyme systems which in themselves are very complex and through which the original components of food are serially processed†. Any deficiency of one or more of the crucial components of these enzyme systems will lead to functional breakdown of the whole serial chain. Adding excesses of non-deficient components will at most effect only a slight overall improvement since no increase in the quantity of limiting factor has been made. In liver damage, a dysfunction of the enzyme systems regulating the blood sugar is as probable as, and indeed is frequently concomitant with, one in the systems regulating other liver functions such as the plasma protein. Since the enzymes controlling the level of the blood sugar and those involved in converting blood glucose to liver glycogen and the reverse are intimately related, one would expect any dysfunction in these systems to be represented by both a hyperglycemia and impaired glucose tolerance. This would mean that ingested glucose would be handled less adequately and more slowly, and that the equilibrium level of glucose in the blood would be set up higher than normal. However, since the deficiency in these systems is not in the amount of insulin present but rather resides in some other limiting component (such as in the actual concentration of an enzyme), administration of the hormone has a relatively small effect on the blood sugar level or glucose tolerance. The systems involved in the metabolism of fat are generally not particularly impaired and since there is no demand for really excessive glucose production

\* Facilities for running the common dye-excretion tests were not available at Cook County Hospital

† For example, the conversion of glucose to glycogen in the liver involves one of these complex enzyme systems rather than a simple enzymatic reaction. The glucose must first be phosphorylated and the phosphorylated units then combined into glycogen. The source of the phosphorylating material is energy-rich phosphate compounds which are in turn generated by the oxidation of the products of intermediary carbohydrate metabolism.<sup>13</sup>

by the liver, no overproduction of acetone bodies is initiated. The alterations in other blood constituents found in this condition are merely indications of the functional breakdown of other liver enzyme systems.

Therefore, since no actual or relative deficiency exists, insulin is not indicated in these individuals. Although a dose of regular fast-acting insulin may overpower the impaired systems and bring the blood sugar down temporarily, no slow-acting insulin will achieve this result. The liver damage does not affect the gluconeogenic systems in such fashion that overproduction occurs. Indeed, if the damage is severe, the reverse may be true. Ketosis may result only if the glucose loss in the urine is so great and dietary carbohydrate so small that gluconeogenesis must proceed at an excessive rate to maintain the blood sugar. Therefore, in these cases insulin plays no part in therapy and may cause harm upon continued administration\*. The proper therapy is a high carbohydrate diet (400–800 grams) which (a) in itself has a restorative effect upon the liver parenchyma and (b) reduces the work of the liver in supplying carbohydrate lost to the body in the urine.

### SUMMARY

1 "Adult" diabetics are shown to differ so markedly from the juvenile type that they are considered as suffering from a distinctly different disease.

2 The dysfunction in the majority of adult diabetics seen by us is demonstrated to be hepatic rather than pancreatic in origin.

3 Therapy directed toward the liver is shown to give far greater success in the management of these patients than insulin administration and a diabetic regime.

We wish to express our gratitude to Dr. Hugo Fenske, Dr. Arthur Zweibel and Dr. Jack Rodriguez for assistance rendered us in the course of this investigation.

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\* It has been reported that excessive insulin administration has led to islet atrophy in rats<sup>14</sup>. But even more important is the effect of excess insulin administration upon the deposition and mobilization of glucose. Soskin has shown that the presence of extra insulin in the blood causes (a) an increased deposition of glycogen in the peripheral tissues and (b) a reduction in the amount of glycogen stored in the liver<sup>15</sup>. This has the effect of reducing the blood sugar level. Furthermore, it causes a redirection of administered glucose away from the liver toward the peripheral tissues. If this carbohydrate is being given to make up for glucose lost in the urine, simultaneous administration of insulin in great measure defeats one's purpose since a large portion of the glucose is converted into non-labile muscle glycogen and the needed replacement glucose must still be formed by the gluconeogenic systems of the liver. In liver damage where a high blood sugar is a necessary part of the therapeutic routine, this is an especially serious effect. The clinical validity of these conclusions is shown by the experiments of Rosenbaum et al., who found that the administration of insulin to normal individuals caused them to show a diabetic glucose tolerance curve for several days indicating that the capacity of the liver to store glucose was definitely below par<sup>16, 17, 18</sup>.

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# CASE REPORTS

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## PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS, REPORT OF CASE \*

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THE effectiveness of penicillin in the treatment of subacute bacterial endocarditis is now under investigation at various centers. Early trials with small amounts of the drug, although discouraging, indicated its ability to sterilize the blood stream temporarily in some instances. The National Research Council<sup>1</sup> reported disappointing results in 17 cases in which the total dosage varied from 240,000 to 1,760,000 Florey units administered over a period of from nine to 26 days. Herrell<sup>2</sup> was unable to influence the course of one case in which the organism was inhibited (in vitro) by penicillin in dilutions of 1:500,000. The total dosage employed, however, was only 128,000 units and the duration of therapy only six days. Herrell observed the reappearance of *Streptococcus viridans* in the blood within four to six hours after administration of penicillin was discontinued. He emphasized that although the blood stream may be temporarily freed of organisms, the persistent focus on the heart valve precludes the successful use of this drug. Similar results with relatively small dosage were recorded by Herrell in a later report,<sup>3</sup> by Florey and Florey,<sup>4</sup> and Dawson and Hobby.<sup>5</sup> The latter authors, however, were successful in the treatment of two cases in which 830,000 units and 1,420,000 units were given over a period of 10 and 33 days respectively. On the other hand, they observed no improvement in two other cases in which 6,670,000 units and 7,960,000 units were administered in 30 and 33 days respectively.

The most encouraging report on penicillin in subacute bacterial endocarditis has come from Loewe and his associates.<sup>6</sup> These workers were successful in arresting the disease in seven of nine patients by employing combined penicillin-heparin therapy. In their opinion heparin "dissolves" vegetations on the heart valves, and permits greater activity of the chemotherapeutic agent. The total dosage of penicillin in their cases varied from 867,920 to 7,890,340 Florey units. The daily dosage varied from 40,000 to 200,000 Florey units and was administered chiefly by the continuous intravenous drip method.

More recently Keefer<sup>7</sup> stated that of 55 cases of bacterial endocarditis reported to the Committee on Chemotherapeutic and Other Agents of the National Research Council, only three were still alive after one year of study. He stated further that several other cases with which he was familiar had received more than 20,000,000 units of penicillin with little or no influence upon the disease.

From these observations it is evident that opinion must be reserved regarding the value of penicillin in subacute bacterial endocarditis until accumulated

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From the Cardiovascular Service, U. S. Marine Hospital.



experience permits an accurate evaluation of this form of therapy. The following case of *Streptococcus viridans* endocarditis appears to have been arrested by this form of treatment.

### CASE REPORT

P. P. T., a 21 year old seaman of Italian descent, was admitted to the hospital on December 4, 1943 with the complaint of fever, weakness and generalized aching in the muscles and joints. His symptoms had begun with a "cold" six weeks previously and persisted in varying degree until the time of admission. He received sulfonamide therapy aboard ship for a period of three weeks without clinical improvement. There was a history of an acute attack of rheumatic fever at the age of five with a persistent murmur of the heart dating from that episode. For a number of years he had suffered from chronic sinusitis with recurrent, acute exacerbations.

Examination revealed a slim, well-developed, listless, young male with a characteristic cafe-au-lait complexion. Temperature was 101° F, pulse 110, respirations 20. The radial pulses were full and bounding, equal and regular. The blood pressure was 125 mm Hg systolic and 0 mm diastolic. The apex impulse of the heart was felt in the sixth left intercostal space in the anterior axillary line. There was a systolic murmur of moderate intensity and a mid-diastolic rumble with presystolic accentuation at the mitral area. At the aortic area and along the left sternal border a high-pitched early diastolic murmur was noted. The lungs were clear throughout. The spleen was palpable three fingers' breadth below the left costal margin. Petechiae were present in the pulps of the fingers and toes and in the left lower palpebral conjunctiva. There was no clubbing of fingers or toes.

Initial Laboratory Data. The blood Wassermann and Kahn reactions were negative. Urine analysis showed normal findings except for a few red blood cells. The blood count revealed 4,500,000 red cells with 14 grams of hemoglobin. There were 11,400 white blood cells per cu mm with 74 per cent neutrophils, 22 per cent lymphocytes and 4 per cent transitionals. The sedimentation rate (Cutler) was 24 mm per hour.

Electrocardiogram showed normal rhythm with a ventricular rate of 90, bifid P-waves in Leads II and IV, P-R interval 16 sec, QRS interval 0.08 sec, tendency to left axis deviation. Bedside roentgen-ray of the chest showed marked enlargement of the cardiac shadow, especially to the left, with prominence of the right auricular border.

Blood culture drawn on December 7 was positive for *Streptococcus viridans*, showing 128 colonies per cubic centimeter of blood.

In vitro tests of the susceptibility of this strain of the organism to sulfonamides showed it to be unaffected even in concentrations up to 30 mg per cent. Sulfadiazine exhibited the greatest inhibitory effect. In vitro studies also showed this strain to be resistant to relatively high concentrations of penicillin.

Inasmuch as penicillin was not available at the time, intravenous medication with the sodium salt of sulfadiazine was begun on December 15. Eight grams of the drug were given at once followed by one gram every four hours thereafter. The temperature returned to normal and persisted at this level for three days. A sulfadiazine blood level of 14.8 mg per cent was reached on the third day, but the development of oliguria and hematuria necessitated the discontinuance of the drug.

Penicillin therapy was begun on December 18 in the dosage of 50,000 units intramuscularly every four hours (300,000 units daily). This amount was employed for two days and then for the next three days the dosage given varied between 65,000 units and 75,000 units every four hours. The total number of Florey units administered in the period of five days was 1,840,000. The patient's temperature remained normal throughout this time except for a single elevation which followed a trans-

fusion of 500 c.c. of blood. Immediately upon the discontinuance of penicillin, sulfadiazine was administered in moderate dosage. Blood culture had been sterile the day penicillin was started and remained so throughout its use. The patient seemed to improve clinically. Fresh petechiae, however, were noted in the left lower palpebral conjunctiva and on the left index finger on December 22. The following day two more appeared in the left palm. Sulfadiazine blood levels were maintained at about 7 mg. per cent until December 30 when the drug was discontinued. On January 4 the spleen was no longer palpable, there were no fresh petechiae, and the temperature was still normal. The following day, however, the patient developed an acute pharyngitis, there was an elevation in temperature and blood culture was again positive for *Streptococcus viridans*, showing six colonies per cubic centimeter of blood. Sulfadiazine was started orally, and by means of supplementary intravenous injections of sodium sulfadiazine a blood level of 15 mg. per cent was attained. Signs of sulfonamide toxicity again developed and on January 14 the drug had to be halted despite a positive blood culture. The temperature had remained normal throughout the course of sulfadiazine, but upon its withdrawal fever again developed. The patient complained of malaise, anorexia, generalized joint pains, and swelling and tenderness under the left eye. No new petechiae were noted, however.

On January 19 blood culture was still positive for *Streptococcus viridans* and on that date penicillin therapy was again instituted, this time by the continuous drip method. The drug was administered throughout the day and night. The 24 hour dosage was 360,000 units dissolved in a liter of normal saline. To the solution of penicillin in saline, 80 mg. of liquaemine was added on the first day, subsequent dosage of liquaemine was 60 mg. every 24 hours. Clotting time by the Lee-White method at the commencement of penicillin-liquaemine therapy was seven minutes. The next day the clotting time was still seven minutes and fresh petechiae appeared in the left lower palpebral conjunctiva. The patient remained quite sick and the temperature varied between 102° F. and 104° F. for the next few days in spite of negative blood cultures. On January 22 dosage of penicillin was increased to 500,000 units per day but the temperature persisted in its elevation. The patient felt cold, sweated profusely and suffered several severe chills. Clotting time remained unchanged. On the afternoon of January 24 the temperature began to climb and reached a peak of 107° F. in the early evening. The heart rate at this time was 190 per minute and the patient appeared extremely ill. He was packed with iced towels for two hours with a fall in temperature to 103.6° F. A fresh solution of penicillin and liquaemine was made up and administered in a carefully sterilized infusion set in an attempt to eliminate possible pyrogenic factors. The temperature, however, rose again to 106° F. during the night and remained at that level until the following morning when the infusion was stopped. With discontinuance of the intravenous penicillin and liquaemine, the temperature immediately dropped to 96° F. and then rose to normal. Penicillin was then administered by intramuscular injection in the dosage of 75,000 units every three hours (600,000 units daily). On January 27 the daily dosage was reduced to 500,000 units per day (62,500 units every three hours), and on this schedule the patient continued to show progressive clinical improvement. His course remained afebrile, and repeated blood cultures were negative. The drug was discontinued on February 3. The only supplementary medication during the penicillin therapy was a blood transfusion. The total dosage of penicillin during the second course of administration was 7,519,000 units over a period of 16 days. Thirteen hours before the last dose of penicillin was given, the administration of sulfadiazine was begun. The blood level was first built up by intravenous injection of the sodium salt and then maintenance dosage was started orally. A level of 5-7 mg. per cent was maintained for a period of three weeks and then the drug was discontinued.

In an effort to combat the chronic sinus infection a nebulizer containing penicillin solution was employed. Patient, when last examined, had gained considerable weight.

and appeared robust. Temperature and pulse rate had remained normal and the blood stream was sterile. Blood picture, urinalysis and sedimentation rate were within normal limits. Subjective and objective improvement had persisted without remission for a period of six months.

### DISCUSSION

The introduction of penicillin again raises the hope that an effective therapeutic agent for subacute bacterial endocarditis may be at hand. Reports in the literature to date, however, offer a confused picture and although numerous failures have been recorded it must be admitted that dosage, method of administration, and duration of therapy have not been satisfactory in many instances. From purely theoretical considerations it would seem that effective therapy demands not only (1) an adequate penicillin blood level to sterilize the blood stream but also (2) a maintenance of this level for sufficient time to permit sterilization and organization of the vegetations on the heart valve. In the case herein reported we were unsuccessful in our first attempt to attain these objectives. Thus it was found that the four-hourly injection of penicillin resulted in an effective blood level only for one and one-half to two hours after each injection. Thereafter, the concentration of the drug fell below the level necessary to inhibit growth of the organism as determined by previous *in vitro* studies. Inasmuch as the duration of treatment was only five days, we attempted to supplement this therapy with sulfadiazine when the supply of penicillin was exhausted. The return of a positive blood culture several days after all therapy was discontinued testifies to the inadequacy of this form of management.

In view of these considerations, the second course of penicillin was initiated by the continuous intravenous drip method in an attempt to maintain a constant effective blood level of this drug. It must be emphasized that heparin was used solely for the purpose of preventing clot formation within the needle and not to increase the coagulation time of the blood as recommended by others.<sup>1</sup> The continuous drip method was employed for five days, at the end of which time sensitization to heparin as manifested by hyperpyrexia necessitated its withdrawal. Penicillin was then administered intramuscularly every three hours in appreciably larger dosage. Blood studies indicated that an adequate level of penicillin was reached and maintained throughout this apparently successful course of therapy.

### SUMMARY

A case is presented in which 7,519,000 Florey units of penicillin, administered over a period of 16 days, were effective in arresting a case of subacute bacterial endocarditis which had not responded to massive sulfadiazine therapy. No clinical or laboratory evidence of bacterial activity has been present for the past six months.

*Addendum.* Physical examination in February 1945, twelve months after discontinuance of penicillin therapy, revealed no evidence of infection. Blood culture was negative.

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## SUBACUTE BACTERIAL ENDOCARDITIS COMPLICATED BY AGRANULOCYTOSIS, REPORT OF CASE WITH RECOVERY

By HENRY I RUSSEK, M D, RICHARD H SMITH, M D, *Staten Island, New York*, and BURTON L ZOHMAN, M D, F A C P, *Brooklyn, New York*

THE superiority of penicillin over all other agents thus far employed in the treatment of subacute bacterial endocarditis appears to be established <sup>1, 2, 3, 4, 5, 6</sup> That penicillin may similarly prove to be an important advance in the therapy of agranulocytosis has been hypothesized on the basis of the low toxicity of the drug combined with its high antibacterial potency <sup>7</sup> Supporting this view is the record of three successfully treated cases already reported in the literature <sup>8, 9</sup>

The occurrence of agranulocytosis in a case of *Streptococcus viridans* endocarditis provided an opportunity for testing the effectiveness of penicillin in both conditions simultaneously The purpose of this paper is to record the first case of recovery from this combination of diseases

### CASE REPORT

F M, a 21 year old white merchant seaman, was admitted to the U S Marine Hospital on May 29, 1944 complaining of fever and joint pains of four weeks' duration Past history was negative except for an attack of rheumatic fever in 1936

Physical examination revealed a typical cafe-au-lait complexion Temperature was 101° F The mucous membranes were pale Petechiae were noted in both lower palpebral conjunctivae Examination of the heart revealed a high-pitched diastolic murmur in the third left intercostal space close to the sternum There was a loud systolic murmur at the mitral area This murmur was transmitted to the axilla The blood pressure was 120 mm Hg systolic and 40 mm diastolic The spleen was palpable two fingers'-breadth below the left costal margin

Roentgen-ray examination revealed a mitral configuration of the heart

Laboratory studies showed a positive blood culture for *Streptococcus viridans* on June 11, 13, 20 and 30 and on July 11, 17 and 24 Blood count on admission revealed

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3,020,000 red blood cells with 50 per cent hemoglobin. There were 12,050 white blood cells with a differential count of 66 per cent neutrophils, 26 per cent lymphocytes, 7 per cent transitionals and 1 per cent eosinophils. Urinalysis showed a moderate amount of albumin and many red blood cells. Sedimentation rate by the Wintrobe method was 28 mm in one hour. Wassermann and Kahn serologic reactions were negative.

On July 11, the patient was given sulfadiazine, 4 grams immediately, and 1 gram every four hours for 14 days. There was no clinical improvement as shown by the accompanying chart (chart 1). Fresh petechiae were noted and the blood culture

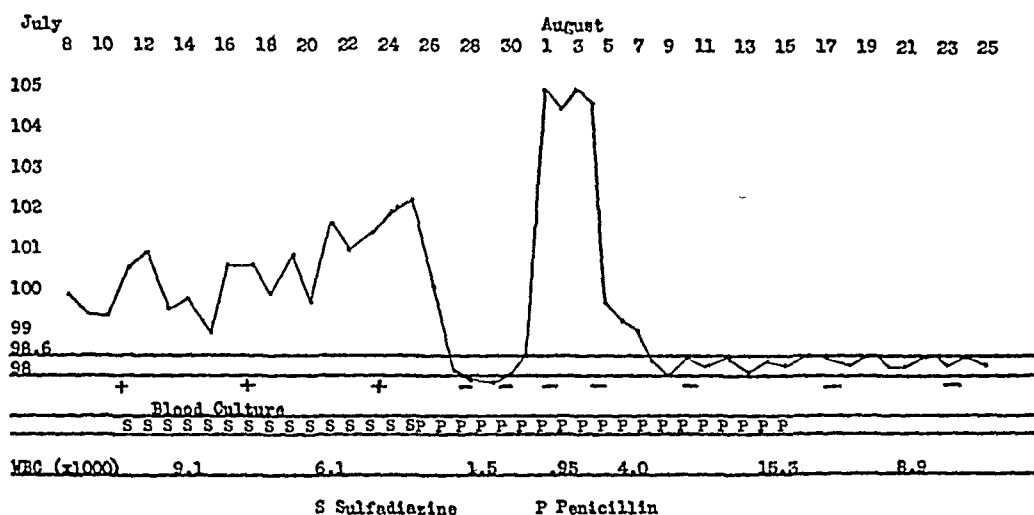


CHART 1

remained positive for *Streptococcus viridans*. A blood count on July 21 revealed 6,100 white blood cells, of which 66 per cent were neutrophils. An erythematous, macular rash appeared over the trunk and limbs and was attributed to drug therapy. On July 25, sulfadiazine was discontinued and a course of penicillin was started in the dosage of 50,000 units every three hours. The temperature returned to normal within 24 hours and there was distinct clinical improvement. Repeated blood cultures were negative. On July 29, four days after sulfadiazine was discontinued, a blood count showed 1,500 white blood cells with 54 per cent neutrophils, 43 per cent lymphocytes and 3 per cent monocytes. The red cell count and hemoglobin were essentially unchanged. Patient gave no history of previous sulfonamide therapy.

On August 1, the temperature rose to 105° F. The throat was mildly congested but there was no lymphadenopathy. The blood picture showed 2000 white blood cells with 89 per cent lymphocytes and 11 per cent monocytes. No granulocytes could be found in the blood smear. Blood culture remained negative. On August 2 there were 950 white blood cells, none of which belonged to the granulocytic series. Beginning on August 3, pentnucleotide (10 cc) and liver extract (15 USP units) were given intramuscularly once each day. Penicillin therapy was continued as before. A transfusion of 500 cc of whole blood was given on August 3 and repeated on the following day. On August 5 there were still no granulocytes in the blood smear. On August 7 the white cell count rose to 4000, the differential count showed 43 per cent neutrophils, of which 23 per cent were band forms. Myelocytes and metamyelocytes also made their appearance (table 1). Congestion of the pharynx subsided and the temperature dropped to normal and remained at this level. Subsequent blood studies showed a normal total and differential count. On August 12 the administra-

TABLE I  
Blood Studies

Date	W B C	Neutrophils		Remarks
		Polys	Bands	
6-11-44	8,550	70%	—	—
7-11-44	—	—	—	Sulfadiazine started
7-14-44	9,100	68%	8%	—
7-21-44	6,100	54%	12%	—
7-25-44	—	—	—	Sulfadiazine discontinued
7-29-44	1,500	54%	—	Penicillin started
8- 1-44	2,000	No granulocytes		Lymphocytes 89%
8- 2-44	950	No granulocytes		Monocytes 11%
8- 3-44	—	—	—	—
8- 5-44	1,450	No granulocytes		Pentnucleotide and liver extract started
8- 7-44	4,000	20%	23%	—
8- 9-44	8,850	34%	22%	Metamyelocytes 6%
				Myelocytes 3%
				Myelocytes 2%
				Premyelocytes 2%
8-12-44	18,150	39%	14%	Premyelocytes 4%
8-12-44	—	—	—	Pentnucleotide and liver extract discontinued
8-15-44	15,300	54%	12%	Penicillin discontinued
8-22-44	8,950	50%	1%	—
10- 6-44	7,650	58%	2%	—

tion of pentnucleotide and liver extract was terminated. On August 15 penicillin was similarly discontinued, the total dosage having been 8,400,000 units over a period of 21 days. The patient has remained clinically well without further treatment. Blood cultures have been persistently negative and the blood picture has remained normal to date.

## SUMMARY

A case of subacute bacterial endocarditis is reported in which agranulocytosis developed as a complication of sulfadiazine therapy. Recovery from both diseases resulted from the administration of 8,400,000 units of penicillin over a period of 21 days.

*Addendum.* Examination 8 months after discontinuance of penicillin therapy revealed no clinical or laboratory evidence of bacterial activity.

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## GUMMATOUS AORTIC VALVULITIS REPORT OF CASE\*

By S H AUERBACH, M D, *Augusta, Georgia*

CHRONIC aortitis is the most common tertiary lesion of acquired syphilis and deformity of the valve with incompetence is a customary sequel. The characteristic aortic lesion is essentially an endarteritis,<sup>1</sup> followed by necrosis and sclerosis of the media. The adjacent vascularized portions of the valve cusps are affected in the same manner.<sup>2</sup> The destructive process rarely approaches the formation of gummas other than microscopic. Thus, Gordon, Parker and Weiss<sup>3</sup> were able to collect only seven adequately described cases of frank gummatous aortitis in the literature to 1942 in a report of three additional cases.

Gummatous destruction of the aortic valve is also rare. Nineteen acceptable cases of gummatous cardiac valvulitis were collected by Sohval<sup>4</sup> in 1935 and he added another. Of these 20 cases, eight involved the aortic valve. Five of these were without microscopic confirmation of the syphilitic nature of the disease. In four the valvular lesions resulted from spread of gummatous processes primarily involving other cardiac structures. Richter<sup>5</sup> reported the ninth case of gummatous aortic valvulitis in 1936 and successfully demonstrated treponemata in the diseased cusps.

We present an additional case of gummatous aortic valvulitis, the second report in which the causative organisms were demonstrated.

### CASE REPORT

K G, a 65 year old Negro male, was admitted to the University Hospital on December 20, 1942, complaining of shortness of breath. He dated the onset of his illness to a time about seven months before admission, when he began to experience some dyspnea on exertion and occasional attacks of swelling of the feet and ankles after standing for long periods. He was able to continue working until one month before admission when exaggeration of the symptoms necessitated rest. Dyspnea now occurred without exertion and seemed worse at night. A physician was called who gave him "drops" for a "weak heart." He felt somewhat improved from the medication but was never entirely relieved. He gave no history of precordial pain or hemoptysis.

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From the Department of Pathology, School of Medicine, University of Georgia, Augusta, Georgia

The record showed four previous admissions to the hospital. The first, in 1929, was for a foreign body in the pharynx and is important in the present study only in the incidental finding of a positive blood Wassermann reaction. In the following years he reported to the outpatient department at irregular intervals for antisyphilitic treatment. In 1930, there were admissions for periurethral abscess and urethral fistula, and in 1934 an admission for a gunshot wound of the right eye for which the globe was enucleated.



FIG 1 General topography of the left ventricle and aortic valve

The past medical history included a vague story of "rheumatism" at 15 years of age, with subsequent irregular recurrences during the spring months. There was a questionable episode of swelling of the ankles at the age of 30. He gave a history of gonorrhea 25 years before his last admission and of a penile sore about 15 years before.

The family history was irrelevant. Both parents died in old age. A long list of siblings was dead but the causes were unknown to the patient. He denied a family history of heart disease or arthritis.

**Physical Examination** He was fairly well developed and nourished. There was moderate respiratory distress, but he was able to lie flat. Respirations were rapid and somewhat labored. The percussion note over the chest was resonant, but there were moist râles over both lung fields. The heart was not enlarged. There was a distinct thrill over the precordium and the heart sounds were all but replaced by a loud, low-pitched, to-and-fro murmur which was most pronounced in the mitral area. The pulse rate was 92 and the rhythm was regular. Blood pressure was 138 mm Hg.



systolic and 90 mm diastolic. There was irregular scarring of the glans and prepuce with multiple fistulas and false passages. There was slight pitting edema of the ankles.

**Laboratory Data.** The red corpuscles numbered 4,200 million and the hemoglobin measured 11.5 gm. The leukocyte count was 8,000 with 62 per cent polymorphonuclears. The urine on admission showed 2+ albumin and numerous leukocytes in the sediment. The blood non-protein nitrogen was 39 mg. Blood Wassermann and Kahn tests were positive. A roentgen-ray plate of the chest showed no cardiac enlargement. An electrocardiogram seven days after admission showed only digitalis effect.

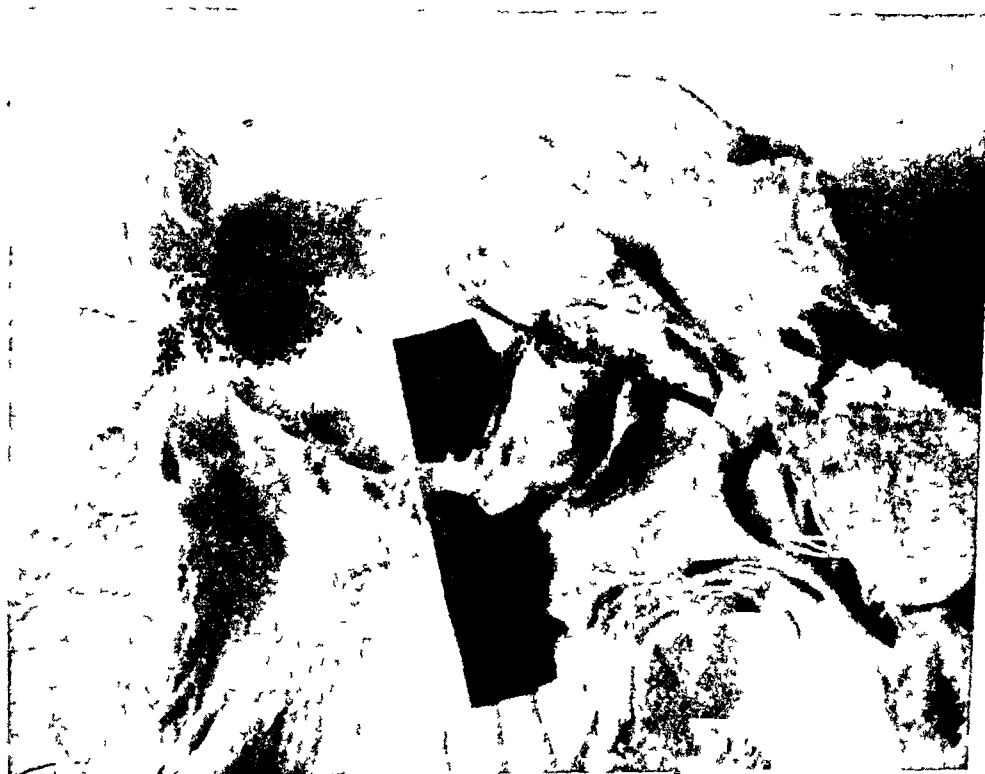


FIG 2 Detail of aortic valve. The slip of black paper extends through one of the large fenestrations.

The clinical diagnosis was Heart disease, probably rheumatic, with mitral insufficiency and stenosis. Two observers mentioned aortic stenosis and regurgitation as possibilities. Under appropriate treatment there was some symptomatic improvement. The respiratory embarrassment was relieved and the urine became normal. The temperature remained flat throughout the period of hospitalization. He complained of some pain on the twenty-first hospital day and died quietly during the afternoon. There was no notable change in physical findings during this period. **Necropsy.** The examination was performed 21 hours post mortem.

The pericardial sac was normal and the epicardium was smooth and glistening. The heart weighed 395 gm, a moderate relative enlargement. Both ventricles were slightly dilated with fluid blood and postmortem clots. The myocardium was soft. The mural endocardium of the left ventricle was slightly thickened. The mitral, tricuspid and pulmonic valves were well preserved and all were competent, these measured 9, 14 and 8 cm respectively. The aortic ring measured 7.5 cm. There was

some general sagging of the cusps so that the coronary orifices were at the level of the free margins (figure 1) Aside from slight fibrous thickening, the left cusp<sup>6</sup> showed nothing unusual The commissural attachment between the right and posterior cusps was disrupted, converting these sinuses into a single chamber (figure 2) That portion of the common leaflet representing the posterior cusp was transformed into a flat thickened yellowish mass measuring 2.2 cm transversely, 1.3 cm perpendicularly and 0.2 to 0.3 cm in thickness The surface was rather irregular and was covered in part with a thin coat of blood and fibrin It was largely detached from the aortic ring by two fenestrations at the base, the larger of these



FIG 3 Photomicrograph of the aortic lesion showing central necrosis and peripheral cellular response Treponemata were numerous in this necrotic area  $\times 200$

windows being 1.5 cm in length (figure 2) Two persistent membranous strips served to connect the remains of the cusp to the ring and to the right cusp The latter showed a small fenestration at the commissural junction There was a small yellowish nodulation on the aortic wall at the junction of the left and posterior cusps

The arch of the aorta was remarkably free from gross evidence of disease There was moderate atherosclerosis of the distal portion Both coronaries showed some sclerosis but both were patent, the orifices were wide

Microscopically, the distal portion of the posterior cusp represented by the yellowish mass showed widespread coagulation necrosis surrounded by a mantle of fibroblasts and numbers of infiltrating plasma cells, macrophages, lymphocytes and polymorphonuclear leukocytes, occasional multinucleated giant cells were present (figure 3) In some areas the necrosis presented a more caseous character and polymorphonuclears were more abundant There was active fibrosis approaching the



FIG 4 The organisms as seen in silver preparations Only a single spirochete is in clear focus  $\times 1290$

base of the valve and leukocytes were fewer in number. At the line of attachment were several entering blood vessels, each surrounded by plasma cells and lymphocytes. The annulus was comparatively unaffected. In the proximal termination of the media of the aorta, however, there was a fairly diffuse infiltration of leukocytes and occasional minute areas of necrosis were present. In a section of the aorta distally, though within the pericardium, there was microscopic evidence of syphilis. The adventitia was fibrotic and the vasa vasorum showed endarteritis with perivascular round cell infiltration. The outer third of the media was involved. Numerous treponemata were demonstrable in the necrotic portion of the valve in silver preparations stained by the Dieterle method<sup>7</sup> (figure 4). None was found in the fibrous portion of the valve nor in the adjacent aorta.

The myocardium showed some hypertrophy of the fibers. No Aschoff bodies were found. The endocardial fibrous thickening of the left ventricle was patchy in distribution and appeared to be of vascular origin. Other lesions of significance in the case were passive congestion of the lungs, purulent bronchitis, chronic pyelonephritis of the right kidney, agenesis of the left kidney, chronic cystitis, chronic prostatitis and early adenocarcinoma of the prostate.

#### COMMENT

We agree with Sohval<sup>4</sup> that "acquired syphilis has not yet been proved to originate in a valve." In all the reported cases of valvulitis, including the present study, evidence of prior or at least concurrent syphilis of an adjacent structure is present and it is reasonable to assume that the more natural site first bears the brunt of disease. Those cases of aortic valvulitis which are fully described were preceded by aortitis (with aneurysm in three) or interventricular septal gumma, and the cusps were involved by simple extension. The case described by Richter<sup>5</sup> and this study have one feature in common which is unusual, namely, an acuteness of the valvular lesion to the extent of overshadowing the underlying aortitis. It is of interest that a disease which characteristically attacks the aorta in a chronic manner and involves the valve only secondarily does rarely reverse its natural history and destroy the valve in a stage when the aortic lesions are comparatively insignificant.

Several possible attenuating factors have been brought out previously but we cannot reconcile this case with the suggestions. Gordon, Parker and Weiss have pointed out the relatively high incidence of combined rheumatic heart disease and gummatous aortitis and raise the question "as to whether rheumatic fever, which is prone to produce an acute cellular hyperergic reaction in the myocardium or in the root of the aorta, enhances the tendency toward the development of gummas, particularly in patients who have received but partial antisyphilitic treatment." Only the latter factor could pertain to this case, despite the presumptive clinical diagnosis of rheumatic carditis, the absence of gross or microscopic evidence of the disease is virtually exclusive. Insufficient and sporadic antisyphilitic treatment is an undeniable possibility as a factor but such self-mistreatment has been common among those of the patient's social stratum whereas cardiac gummata have remained extremely rare. Norris<sup>8</sup> and others have mentioned youth as an element which might influence the course of events. This patient was 65 years old, and was known to have had syphilis for 13 years and had probably been infected for at least 15 years. Nor was there a preexisting valvular defect as in Richter's case (congenitally bicuspid valve

and subaortic stenosis) which could conceivably influence the development of such a lesion

Clinically, gummatous valvulitis is of little practical importance because of its rarity. The diagnosis has not been established ante mortem and no signs of sufficient constancy to suggest the diagnosis have been noted. The signs and symptoms, as well as other data, vary with the location and nature of the "primary" lesion. It does, however, constitute a possibility to be borne in mind with puzzling cardiac disease occurring in syphilitics.

### SUMMARY

The twenty-second case of gummatous valvulitis is reported, the tenth case involving the aortic valve, and the second in which the causative organisms were successfully demonstrated.

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## FULMINATING PURPURIC MENINGOCOCCEMIA (WATERHOUSE-FRIDERICHSEN SYNDROME) WITH RECOVERY \*

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RECOVERIES in cases of fulminating purpura of infectious origin, the so-called Waterhouse-Friderichsen syndrome,<sup>1</sup> are extremely infrequent. Of 130 cases of the disease collected from the literature to October 1943, we have been able to find but five cases not ending fatally<sup>2, 3, 4, 5, 6</sup>. We should like to add a sixth case of recovery.

\* Received for publication January 15, 1944

From the Department of Medicine of the Beth-El Hospital, Brooklyn, N Y

## CASE REPORT

G R, an adult white female, the hospital bacteriologist for 15 years, was admitted to the Beth-El Hospital late on the morning of March 4, 1943. On the preceding day she had, late in the afternoon, complained of being somewhat tired but at that time showed no pyrexia, and superficial physical examination was negative, in particular there was no purpura nor cyanosis. She left the hospital at 7 p m that day planning to attend a scientific meeting that night. Two hours later she suddenly experienced a series of chills, each of a few minutes' duration, the entire series lasting over a period of about half an hour. Rectal temperature taken at that time was 101° F. Examination by an ambulance surgeon was entirely negative save for an intense congestion of the pharynx, marked cyanosis of the lips, and a moderate diffuse dusky-ness of the body, no purpura was present, pulse was not rapid and of good quality. Grippe was suspected and hospitalization advised, but this was refused because of the severe snowstorm then raging. The remainder of the night was spent in sleeplessness in spite of marked drowsiness, frequent severe chills, and an intermittent but increasingly more marked sense of abdominal fullness and pressure, relieved at first for short intervals by dribbling urination. Toward morning the abdominal pain had become very severe and cramp-like. She was totally unable to void. She remained conscious and rational throughout this period, issuing instructions as to some of her possessions just prior to her removal, by ambulance, to the hospital at 11 a m. She even insisted on dressing herself and walking, with but slight assistance, to the vehicle.

Her health prior to the present episode had always been good save for a long-standing localized skin induration of both mid-anterior tibial regions, diagnosed by biopsy as atypical scleroderma. This condition had shown no progression for the last five years. During the last seven years she had shown occasional red cells and a very rare hyaline cast in centrifuged urinary specimens, and had constantly maintained a blood urea nitrogen level in the vicinity of 21 mg per c c. Several urea clearance tests showed 75 to 85 per cent standard clearance. Blood pressure was never higher than 150 mm Hg systolic and 74 mm diastolic. Her skin capillary resistance was apparently considerably reduced, the tourniquet (Rumpel-Leede-Hess) test showing never less than 50 and on several occasions as many as 200 petechial spots. The last such test was performed about two years prior to the present illness and showed 100 petechiae. Extensive investigations failed to reveal any allergic factors, numerous hematologic studies failed to show any evidence of blood dyscrasia, her diet was not deficient in vitamin C, and the administration of large added amounts of vitamin C and of vitamin P did not apparently affect the results obtained on tourniquet test, nor the microscopic urinary findings. She did not bruise easily. No focal infection was ever found. It was believed that she had a fragile capillary system of unknown etiology, that this probably accounted for the urinary findings, that there was no apparent progression of the process, that it was probably clinically of no significance, and that no treatment was necessary. Throughout this entire period she had been carrying on her extensive routine and research work without difficulty.

Admitted to the hospital some 10 minutes after leaving her home, she was still conscious, but lapsed suddenly into coma while talking to the interne who had just obtained a fragmentary statement as to her present illness. Temperature at this time was 105.4° F, pulse 110, very feeble, easily compressible, and with frequent extrasystoles, respiratory rate 30. Blood pressure was 90 mm Hg systolic and 60 mm diastolic. There was no nuchal rigidity, all reflexes were somewhat sluggish but equal, and there were no pathologic reflexes. A massive purpuric rash was diffusely scattered over her abdomen, and to a lesser extent, her chest and back, on her arms and legs, particularly around the wrists and ankles, a similar coarse and fine purpuric rash was present. The hemorrhages ranged from bright red to purple, were entirely macular and serpiginous, were not ulcerated, and were sharply defined though fre-

quently confluent or grouped. Both the ecchymoses and the petechiae showed an underlying and surrounding bluish or purplish tint not disappearing on pressure. On the hard palate four similar blue-red hemorrhages were present. The lips were cyanosed deeply, the remainder of the body of an ashen hue. The body was hot, the extremities cold. Heart sounds were rapid, distant, and very feeble. Lungs were clear, respirations shallow. Abdomen was slightly distended, soft, and tympanitic, no viscera were palpable, the splenic dullness was not increased. Catheterized urine showed a faint trace of albumin, an occasional red cell and hyaline cast. Blood count showed 3,700,000 red cells, 11.5 gm hemoglobin, 250,000 platelets, 17,000 white cells of which 1 per cent were myelocytes, 47 per cent metamyelocytes, 11 per cent staff neutrophils, 25 per cent segmented neutrophils, 12 per cent lymphocytes, 1 per cent Turk cells, and 3 per cent monocytes, no toxic granules were present.

Five cubic centimeters of digifoline and an equal amount of caffeine sodium benzoate were immediately administered hypodermically, 4 ounces of coffee and 2 grams of sulfadiazine were given by gavage. One hour thereafter 5 grams of sodium sulfadiazine in 100 c.c. normal saline were administered intravenously. Her blood pressure meanwhile had fallen to 60 mm Hg systolic and 50 mm diastolic, despite further digifoline-caffeine and coramine therapy, and one hour after the intravenous injection had been completed both the blood pressure and the peripheral pulse were unobtainable. At this time, the coma was most profound and very slight resistance of the neck was present. Her back and buttocks had taken on a pronouncedly mottled appearance resembling postmortem lividity and similar areas were noted on the posterior thighs, ankles, and over the deltoid regions.

At 5 p.m., six hours after admission, 10 c.c. of adrenal cortical extract (Upjohn) and 1,000 c.c. of 10 per cent saline containing 5 grams of sodium sulfadiazine were administered intravenously at the rate of 30 drops per minute. Seven hours later 1,000 c.c. of 5 per cent glucose in normal saline containing 10 c.c. of adrenal cortical extract were similarly administered. One gram of sulfadiazine was given by gavage every four hours. On the morning after admission, the temperature had fallen to 99.8° F, the pulse was 108, regular and of fair quality, and the blood pressure was 70 mm Hg systolic and 50 mm diastolic. That afternoon the temperature had further fallen to 98° F, thereafter it slowly rose to between 100° and 101° F for the six days during which oral sulfadiazine was continued, receding to 98.6° F as soon as the drug was discontinued.

By morning of her second day in the hospital the patient was again conscious and rational, thereafter slowly recovering from a very profound weakness and an asthenia so severe that attempting to stand was difficult three weeks after admission. The adrenal cortical extract, 10 c.c. daily in two divided doses intramuscularly, was continued for four days, she received in all 60 c.c. of the extract, a third of this during the first 18 hours of her stay. On the afternoon of her second day in the hospital (by which time she had received 20 c.c. of adrenal cortical extract and 180 grams of sodium chloride intravenously) the blood pressure was 92 mm Hg systolic and 70 mm diastolic. On the third day, and thereafter until the twelfth day, the blood pressure was 120 mm Hg systolic and 70 mm diastolic, on the twelfth day it was 146 mm systolic and 80 mm diastolic, on the thirteenth day and thereafter until discharge on the twentieth day, it was 150 mm systolic and 80 mm diastolic. Two months after her discharge, and again on numerous occasions thereafter until this report, nine months after discharge, it remained at the level last noted in the hospital.

Oral sulfadiazine, 1 gram every six hours, was continued until the seventh day of her hospital stay, in all, she received 39 grams of the drug, 15 grams of this in the first 24 hours, 10 grams of which were given intravenously. Red cells and occasional granular and hyaline casts were noted in all urinary specimens from the third to the twelfth day. Acetylsulfadiazine crystals were noted only on the fourth and

fifth days Urinary output and analyses, and blood chemical determinations are noted in table 1

The purpuric rash began to fade from the body and extremities within the first 24 hours, had completely disappeared by the fourth day, and left no residual skin changes The oral hemorrhages ulcerated on the eighth day, but had completely healed, upon the application of gentian violet locally, by the twelfth day On the

TABLE I  
Urinary and Blood Chemical Findings, Case of Waterhouse-Friderichsen Syndrome

Date	Fluid Intake	Urine				Blood					Chloride (mg %)
		Output	Sp Gr	Alb	Casts	Sulfadiazine (mg %)	Urea (mg %)	Total Protein (gm)	A G ratio	Sodium (meq L)	
3/4	1700	450	1018	2+	hyaline 4+						
3/5	2140	1480	1012	3+	hyaline 1+	25.3	49.5	6.28			
3/6	2580	1090	1020	4+	hyaline 4+	17.0	37.5				
3/7	1380	840	1022			5.6	22.2				
3/8	1530	1140	1012	3+	hyaline 4+						
3/9	1500	1920	1010	2+	granular 1+						
3/10	1210	3750	1006	0	0						
3/11	1950	1680	1012								
3/12	1980	1240	1012								
3/13	1710	1500	1018								
3/14	1260	1400	1014								
3/15	1410	1950	1010	0	0						
3/16	1200	1860	1010	2+	granular 1+		34.0	5.2	2.13.1		
3/17	1200	1280	1010	2+	0						
3/18	1680	980	1020								
3/19	790	990	1018	ft	granular 1+						
3/26			1018	0	0		21.0	6.2	3.42.8		
5/25			1016	0	0		21.4	6.8	4.82.0	136	512

seventh day a crop of herpetiform vesicles appeared on the neck just below and to the right of the mandibular symphysis, these slowly dried and were gone by the seventeenth day

A blood culture taken on admission showed a heavy growth of *Neisseria intracellularis* (meningococcus) type 1 on the second day Subsequent blood cultures were sterile Direct smears from the hemorrhagic skin lesions showed intracellular Gram-negative diplococci Spinal tap was never performed since, with the exception of the transient nuchal rigidity appearing on the day of admission and disappearing within five hours, no neurological signs were ever noted

Diffuse pitting edema of the legs and thigh was noted on the twelfth day and coincided roughly with a rise in blood urea nitrogen, diminution in total protein, and slight inversion in the A G ratio The protein content of her diet was increased to 200 grams, and the edema slowly disappeared, was completely absent by the twentieth day At this time the blood urea nitrogen level was normal, the blood protein level elevated to 6.2 grams, the A G ratio 3.42.8 Two months after discharge, the blood protein level was 6.8 grams, the A G ratio 4.82.0 (table 1) No further edema was noted

No blood sodium or chloride determinations were performed while the patient was in the hospital Two months after discharge, the blood sodium was 136 meq/L, the blood chlorides 512 mg per cent These determinations were performed at this time, and will be repeated periodically, in an attempt to evaluate whether the adrenal glands have suffered any permanent damage Hematologic studies performed during the acute illness and two months after leaving the hospital are summarized in table 2



TABLE II  
Hemograms in Case of Waterhouse-Friderichsen Syndrome

Date	RBC (mil lion)	Hgb (grams)	Platelets	WBC	Myelo cytes (%)	Meta myelo cytes (%)	Staff cells (%)	Seg mented cells (%)	Eosin ophiles (%)	Lymph ocytes (%)	Mono cytes (%)	Turck cells (%)	Toxic Gran ules (% WBC)
3/4	3.7	11.5	250,000	17,000	1	47	11	25		12	3	1	none
3/6	3.7	11.5	250,000	24,000	4	52	11	29		3	1		100%
3/8	3.4	10.5	260,000	13,000	3	35	10	22	3	24	3		80%
3/10	3.5	10.5	270,000	13,500	0	15	15	40	3	23	4		70%
3/16	3.7	11.0	270,000	9,600	0	0	5	60	0	27	8		20%*
3/24	3.6	11.0	270,000	6,600	0	0	3	61	1	30	5		none
5/25	3.9	12.4	290,000	6,800	0	0	0	74	1	21	4		none

\* All the staff cells and some segmented cells showed toxic granules

Upon discharge from the hospital on the twenty-first day after admission, there were no residual evidences of the infection nor, with the exception of considerable asthenia, any suggestion of adrenal involvement. No neurologic or mental changes were present—the patient had, in fact, been advising her assistants in the laboratory technically for a week prior to her discharge, had been examining cultures grossly while in bed—and careful examination of the cardiovascular and urinary systems failed to show any evidence of functional impairment. Two months after her discharge she was back at both her routine and experimental work in the laboratory, the asthenia having totally disappeared.

#### COMMENT

As has frequently been pointed out, a positive diagnosis of adrenal hemorrhage can be made only at autopsy. So uniformly characteristic, however, are the clinical signs and symptoms of fulminating purpura with adrenal hemorrhage, the so-called Waterhouse-Friderichsen syndrome, that a presumptive diagnosis is warranted clinically. If suspected and vigorously treated, dramatic recovery may be achieved in this condition in which until Carey's report<sup>2</sup> in 1940, a fatal outcome appears to have been invariable.

It is not the purpose of this paper to discuss in detail the pathology of the syndrome. Parenthetically it may be noted that the vast majority of proved cases of Waterhouse-Friderichsen syndrome showed extensive hemorrhagic infiltration and massive disorganization of the adrenal glands. Even in those cases showing at autopsy relatively insignificant adrenal hemorrhages, as in the cases of Gordon and Shimkin<sup>8</sup> and of McLean and Caffey,<sup>9</sup> there appears to have been considerable cortical cellular necrobiosis. This necrobiosis, to which little attention appears to have been devoted in the English literature, was strikingly seen by one of us (M. J.) in a fatal case of the disease showing no significant adrenal hemorrhages. To a lesser degree, these can be seen in the adrenal glands of any severe septicemic state in which a clinical picture of circulatory collapse supervenes. It consists of cellular swelling, the total or almost total depletion of cortical lipoids, and varying degrees of cortical nuclear rhexis. In any event, review of the autopsied cases of Waterhouse-Friderichsen syndrome, with or without adrenal hemorrhage, yields morphologic evidence of adrenal insufficiency. According to Herbut and Manges<sup>10</sup> most authors agree that it is the adrenal insufficiency rather than the toxicity that is responsible for the fatal outcome.

The indications for chemotherapy directed toward the infectious agent, which is usually the meningococcus,<sup>10</sup> although various other microorganisms have been reported as etiologic agents, are usually self-evident. Such chemotherapy needs no discussion at this point except to emphasize that it should be vigorous. Of equal importance is therapy directed at tiding over the apparently functionless adrenal glands. This phase will be discussed in detail.

As pointed out by Carey,<sup>2</sup> adrenalin plays no part in the treatment. It may, as in the case of Rucks and Hobson,<sup>6</sup> be useful temporarily in restoring circulatory and respiratory effort. Even in their case, however, the simultaneous use of artificial respiration and a resuscitator makes difficult the evaluation of the adrenalin. In our case, as in the case of Sharkey,<sup>5</sup> no adrenalin was used\*, nor did the digifoline, caffeine, or coramine administered prevent the rapid progress of circulatory collapse prior to the use of adrenal cortical extract.

Vitamin K plays no rational part in the therapy. Although occasional small hemorrhages do occur in the liver in cases of Waterhouse-Friderichsen syndrome, and cloudy swelling of the hepatic parenchymal cells, slight cellular infiltrates<sup>11</sup> and distortion of the normal radiating structure<sup>10</sup> have been noted, these are not more marked than in any severe systemic infection without bleeding, and no evidence has yet been adduced that any changes in hepatic function relative to thrombinogen exist. In our case a blood prothrombin time (Quick method) at the height of the clinical bleeding showed a normal figure of 13 seconds (control 12 seconds). Perusal of the case of Rucks and Hobson<sup>6</sup> fails to reveal any convincing clinical evidence that the synthetic vitamin K (Synkamine) used in any way altered the course of the disease. No prothrombin determinations were made in that case.

The dramatic improvement in our patient's condition, the rapid change from cold to warm extremities, and the rapid disappearance of the postmortem-like lividity following the intravenous administration of the adrenal cortical extract (a procedure apparently first suggested by Goldzieher and Greenwald<sup>12</sup> but not used by them) impressed us sufficiently to feel that replacement therapy should be instituted in this manner rather than intramuscularly. The detailed account of Carey's case<sup>2</sup> suggests that he too felt as we do, since first signs of improvement appeared after intravenous rather than intramuscular injection of the extract. On the contrary, Rucks and Hobson,<sup>6</sup> using the intramuscular route, did not obtain so smooth a recovery from the signs of adrenal failure but met with several episodes suggesting recurrent adrenal insufficiency and were forced to shorten very materially the interval between doses of the extract. We believe further that large and probably excessive doses of the adrenal cortical extract should be given intravenously during the critical stages and that these be supplemented by intramuscularly injected extract to maintain through slower absorption the beneficial effects. Of equal importance is the use of large amounts of sodium chloride and of fluids, a regimen fully recognized in the treatment of the crises of Addison's disease. Although no sodium determinations were made in our case during the acute illness, a similar determination in another case (in which, as in the present case, there had been no vomiting) seen shortly before

\*The case of Bickel<sup>3</sup> was not available to us. The paper of Grace, Harrison and Davie<sup>4</sup> mentions a case of recovery but cites no details or mode of therapy, the citation being incidental to a general discussion of the syndrome and the report of several fatal cases with autopsy findings.

this one and terminating fatally within one hour after admission to the hospital and before therapy could be instituted, gave a very low value for sodium, 121 meq/L (normal level in this laboratory being 135 to 145 meq/L, by the modified Butler method<sup>13</sup>) This value, as well as a similarly low one cited in the case of Sharkey,<sup>5</sup> the only such studies that seem to have been made in cases of the syndrome, bear out the suggestion of Aegerter<sup>14</sup> that sodium determinations be used as confirmatory evidence of adrenal hemorrhage in suspected cases, a suggestion questioned by Carey<sup>15</sup> who felt that the disease was of too short duration materially to affect the sodium level. Whether any resultant edema may be due to the excessive cortical extract therapy<sup>15</sup> or, as we believe in our case (because of the latent period of development and the simultaneous blood protein changes), is nutritional, is of little moment. In the Waterhouse-Friderichsen syndrome one is dealing with a condition so grave and so rapidly fatal that all other metabolic disturbances are purely secondary, to be dealt with after the patient has been tided over the first few days. In the four previous cases seen by us, death had ensued within 24 hours of onset of symptoms. This statement as to cortical extract therapy does not imply that other symptomatic and shock-combative measures are not to be used. We believe, however, that all these should be subordinate to the adrenal cortical extract and saline therapy. We feel further that it is advisable to continue cortical extract therapy for some time after the disappearance of signs of circulatory collapse, a procedure also followed by Sharkey<sup>5</sup>. Particularly is this important when it is remembered that the infection, localizing in the meninges or serous membranes in other parts of the body or in viscera (such as the heart valves), may remain clinically dormant for several days or longer, only to become clinically active again if chemotherapy is relaxed, a series of events we have seen on several occasions. Should this occur after adrenal cortex replacement therapy already had been discontinued recurrence of the Waterhouse-Friderichsen syndrome might take place even though the evidences of infection be slight. It is for this reason that we continued the sulfadiazine therapy also for seven days, long after all clinical evidence of the infection had vanished save for the continued leukocytosis, the presence in the blood smears of immature leukocytes and toxic granules, and even in the face of a sulfadiazine fever and evidences of renal irritation. The case of Rucks and Hobson<sup>6</sup> illustrates the recurrent phases of the infection and the possibility of recurrences of adrenal insufficiency.

Of interest in our case was the behavior of the peripheral blood cells. So fulminant was the infection that the peripheral blood formula was that of extreme immaturity, a formula that persisted for at least five days after all other evidences of the infection had disappeared. Not until 11 days after the complete clinical subsidence of the infection did the blood picture become approximately normal. Even at this time toxic granules, not present at the height of the infection but appearing as the infection waned, were still present in large numbers. That these changes were not in any way attributable to the sulfadiazine therapy is suggested by the absence of significant changes in erythrocyte or hemoglobin values, and the absence of clinical or laboratory evidences of hemolysis. Whether or not extensive hemorrhages in the bone marrow, found by us in two other cases of the syndrome coming to autopsy, play any part in the blood picture cannot be said.

That the infecting organism did not significantly reach the central nervous

system in our case is suggested by the almost total absence of neurologic signs or symptoms, a finding common to most of the recorded cases of the syndrome.

No substantial reason has yet been advanced for the development of the Waterhouse-Friderichsen syndrome, nor has any complete explanation been given for the occurrence of the massive adrenal, cutaneous, and parenchymal hemorrhages noted in the disease. Schrader<sup>16</sup> and Brunner<sup>17</sup> suggested that thrombosis of the adrenal veins brought about the adrenal hemorrhages, a finding not since reported. It has been suggested<sup>18</sup> that the extraordinary fineness of the adrenal vessel walls in the newborn, associated with venous congestion in the course of difficult prolonged labor, may account for the greater frequency of suprarenal hemorrhage in infants. In infants, it has further been suggested<sup>19</sup> that the adrenal medulla, while undergoing involution, has a rich supply of capillaries and, therefore, readily lends itself to trauma by a variety of agents. Such capillaries and involutional changes do not exist in the adult, for which reason recourse has been had to the theory of selective action of meningococci for structures of ectodermal origin,<sup>19, 20, 21</sup> or the syndrome has been linked with the highly controversial subject of status lymphaticus<sup>21, 22, 23</sup>. As to the former theory of the pathogenesis in adults, no evidence has been presented, as to the latter, there exists, specifically in the cases of the Waterhouse-Friderichsen syndrome, considerable clinical and pathologic evidence to the contrary. This evidence is best presented in the papers of Kunstatter<sup>19</sup> and of Herbut and Manges<sup>10</sup>. It may be that the capillary disorder so long present in our patient and of such marked degree was a factor in causing the massive bleeding noted, that these capillaries, long showing evidence of lowered resistance, broke down under the strain of the severe systemic infection, with the resultant hemorrhages, and that hemorrhages occurring in the adrenals gave rise to the clinical syndrome. The apparent paucity of cases of fulminating purpura of infectious origin, especially in adults, in the face of so many severe septicemic infections, makes probable the presence of some unusual vascular factor, as noted in our case, and should be looked for in future cases that recover from the disease. The factor of reduced capillary resistance persisted in our case though apparently much less pronounced. The last tourniquet test, performed two months after her discharge from the hospital, showed 25 petechial hemorrhages. Concomitantly, the skin lesions noted on the legs for many years disappeared and the urine remained consistently free from red cells since the patient's recovery from the acute infection. We cannot account for this apparent improvement in the state of the capillaries. It may be that the severe shock to the organism improved the capillary tonus in some undetermined manner.

In this year of high incidence of meningococcus infections (for New York City almost as many cases had been reported for the first three months of 1943 as for the entire year of 1942),<sup>24</sup> it is impossible to trace with certainty the source of infection in our case. The only direct contact with the organism that we can determine was a series of cases admitted to the hospital during the months of January and February 1943, the spinal fluids of which our patient examined. She was last in contact with a positive spinal fluid on February 15, 1943, 17 days before she contracted the disease. With the incubation period of the disease so indefinite and ranging from two days to eight weeks, it is manifestly impossible to exclude these contacts. Nevertheless, it should be pointed out that the patient was a very careful technician and a highly skilled bacteriologist,

and one who, despite daily contacts with virulent pathogens over a period of 22 years, had never contracted even the slightest local or systemic infection

No attempt has been made in this paper to describe the clinical manifestations of the syndrome. Our case followed the conventional pattern. Excellent descriptions and statistical analyses of signs and symptoms have appeared, especially in the reviews of Aegerter,<sup>11</sup> Sachs,<sup>22</sup> and recently of Lindsay and associates.<sup>25</sup> The disease is easily recognizable once seen or kept in mind. Even in cases recognized apparently after an interval and after other diagnoses had been entertained,<sup>8</sup> vigorous adrenal cortical replacement therapy yields clinically encouraging results. In fact, such a case, though terminating fatally, might well have been considered as one of recovery from the Waterhouse-Friderichsen syndrome, death apparently resulting from an intercurrent massive pneumococcal pneumonia that complicated the meningococcemia. In this case also there occurred the only recorded instance of pituitary necrosis. Whether this finding is sufficient to warrant the addition of pituitary hormones to the therapeutics of the syndrome is a matter for future study. Very useful in the diagnosis in doubtful cases is the recognition of bacteria in direct smears from the purpuric eruptions as first suggested by McLean and Caffey<sup>9</sup>; this was done in our case. The value of this simple and rapid procedure is emphasized by the recent pathologic studies of Herbut and Manges.<sup>10</sup>

Although the syndrome has become generally known as that of Waterhouse and Friderichsen,<sup>1</sup> it should be pointed out that the first case, complete with autopsy findings, was reported by Voelcker<sup>26</sup> in 1894, that isolated cases were subsequently reported by numerous authors (noted by Waterhouse, who found 15 cases in the literature up to the time of his own paper in 1911), and that the syndrome seems clearly to have been recognized and associated with adrenal hemorrhage and bacterial infection by Little<sup>27</sup> and by Andrews.<sup>28</sup>

## SUMMARY

1 A non-fatal case of fulminating meningococcemic purpura (Waterhouse-Friderichsen syndrome) is reported and the five previously recorded recoveries from the disease are briefly discussed.

2 The role of large doses of adrenal cortical extract and saline in the treatment of the disease is stressed. It is suggested that the intravenous route be used during the acute phase and that replacement therapy be continued for some time after improvement in the blood pressure levels. Chemotherapy should be used vigorously, due allowance being made for latent infection and the possibility of recrudescences.

3 It is suggested that neither adrenalin nor vitamin K plays any essential part in the therapy. Adrenalin may be of value as a temporary cardiorespiratory stimulant when cardiac arrest occurs, but is not to be considered as a specific agent because of the adrenal involvement.

4 The rôle of a deficient capillary system, long present in our patient, is pointed out as a possible factor in the pathogenesis of the disease. It is suggested that further cases of recovery be studied from this point of view.

5 A lowering of the blood serum sodium values occurs in the syndrome. It is suggested that this determination may be useful in the differential diagnosis of adrenal damage in cases of infectious purpura.

6 The demonstration of organisms in direct smears from the purpuric areas is stressed as a rapid diagnostic aid

We should like to express our thanks to Miss Elsie Kaye, Miss Elsie Weidman, and Mr Alvin Dubin, of the department of pathology, for their painstaking laboratory studies respectively of the hematologic, bacteriologic, and chemical phases of this case

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Since our paper was submitted for publication, eight additional cases of the Waterhouse-Friderichsen syndrome eventuating in recovery have appeared in the literature. All received chemotherapy (sulfadiazine or penicillin) and large amounts of adrenal cortex extract and saline. These cases are recorded in the following papers:

- PLABODY, S D *New England Jr Med Sci*, 1943, ccxxx, 934 (one case)
- BUSH, F W, and BAILEY, F R *Ann Int Med*, 1944, xx, 619 (two cases)
- OSBORNE, J, ARNONE, W H, and LYTHCOTT, G H *New England Jr Med Sci*, 1944, ccxxxi, 868 (four cases)
- LOVITTE, A A *Kentucky Med Jr*, 1945, xliii, 24 (one case)

We have ourselves treated two additional identical cases in identical manner save for the substitution of penicillin for sulfadiazine, with uncomplicated recovery.

Bush and Bailey (cited above in note) also confirm the presence of low serum sodium values in cases of the syndrome.

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## CANDIDA ALBICANS (MONILIA ALBICANS) INFECTION WITH BLOOD STREAM INVASION, REPORT OF A CASE WITH A STRAIN CLINICALLY RESISTANT TO SULFONAMIDE DRUGS AND TO PENICILLIN IN VITRO

By STANFORD WESSLER, M D, and HAROLD R BROWNE, M D,  
*Albany, New York*

THE following case is reported because of renewed wartime interest in fungus diseases and because of the comparative rarity with which *Candida* has been found in the blood stream.

The ubiquity of human moniliasis is more fully appreciated today than in former years. Keiper<sup>1</sup> concluded that 3 per cent of apparently normal individuals harbor monilia in their throats. Schnoor<sup>2</sup> has commented on the high incidence of monilia in normal stools. Systemic infection is not rare, as evidenced by reports in the literature of involvement of the bone, lungs and parenchymatous organs with this fungus. Despite this fact, however, up to the present time, few cases of blood stream moniliasis have been reported. Only five instances were found in the literature,<sup>3, 4, 5, 6</sup> all occurring in drug addicts, all ending fatally, and all showing mycotic endocarditis at autopsy. In four patients

\* Received for publication January 12, 1944.

From the Medical Service, Albany Hospital, Albany, New York.

the organism was identified as *Candida parakrusei*, in the fifth as *Candida guilliermondii*

In the case to be presented, the patient was not an addict, so that the introduction of the fungus into the circulation by hypodermic needle puncture can be excluded. The organism isolated was *Candida albicans*, and instead of a fatal termination, a temporary remission occurred.

#### CASE REPORT

T. D., a 43 year old white railroad worker, was in fair health until January 6, 1943 when, following exposure to cold and rain, he developed coryza, cough productive of whitish sputum, fever, sweats and malaise. These symptoms continued despite treatment with sulfathiazole and on the second day prior to hospital entry, January 23, were associated with severe dyspnea, orthopnea and wheeze. He had not had chills, chest pains or hemoptysis.

During the preceding 20 years, following acute respiratory infections, the patient had had occasional coughing spells associated with dyspnea. For the last four years the attacks had been more severe and had been accompanied by an audible wheeze. The past history was irrelevant except for "athlete's foot" in 1935 followed by a mild leg infection. The left hand was amputated at the wrist in 1919 after an accident. For the past five years the patient had had marked polydipsia (drinking over 1½ gallons of water per day) and marked urinary frequency (20 times per day). These symptoms were never satisfactorily explained.

The patient's wife had had a non-productive cough for six months.

On admission the patient appeared flushed, dyspneic, orthopneic and was sweating profusely. The temperature was 102° F. The pharynx was diffusely reddened, the tonsils were enlarged and appeared chronically infected. Respirations were shallow, 38 per minute, but there was no splinting. The anteroposterior diameter of the chest was enlarged, and there were sibilant and sonorous râles throughout both lungs. The heart did not appear enlarged, sounds were distant. There was a sinus tachycardia (140 per min.), there were no thrills or murmurs. The abdomen was slightly distended, but no masses or tenderness were noted. The remainder of the examination was negative except for the healed stump of the left arm.

*Course.* The patient appeared acutely ill on admission and it was thought that he had acute tracheobronchitis. The urine showed 1 plus albumin, 2 plus acetone. The leukocytes numbered 9,100, with 82 per cent neutrophils, 2 per cent eosinophils and 16 per cent lymphocytes, the erythrocyte count was 4,630,000, hemoglobin 16.5 grams. Non-protein nitrogen of the blood was 25 mg per cent.

Several hours after admission the patient was in severe respiratory distress. The vocal cords were edematous, and adrenalin and oxygen were administered with some relief. Twelve hours after entry the patient became increasingly resistant and disoriented, and continued to raise large quantities of thick, tenacious, mucoid sputum. Sodium amytal was given intravenously to quiet the patient.

On the second day, January 24, the admission throat and sputum cultures were found to contain a variety of microorganisms, chiefly pneumococcus type XIX, hemolytic and non-hemolytic streptococci and an unidentified yeast. The patient's temperature was now 103° F. A blood culture was taken and sulfadiazine and fluids were started intravenously. Within 24 hours the patient's temperature and symptoms began to subside, the temperature became normal after 48 hours of chemotherapy and so remained throughout the balance of the hospital stay. Fluid balance was good, satisfactory drug levels were obtained, and by the fifth day (February 28) the patient, except for mild cough, was asymptomatic. Chest films on January 23, January 25



and January 26 (including lateral view) revealed nothing beyond generally and symmetrically increased markings. Repeated urine examinations were negative. The blood examinations remained essentially unchanged.

The blood culture of January 24 yielded 16 colonies per c c of a yeast-like microorganism. This microorganism was not immediately identified, but was believed to be a species of *Candida*. Sputum culture January 26 was also positive for the same microorganism. A blood culture on January 26 yielded 12 colonies per c c and a culture on January 28 yielded 22 colonies per c c, both in 48 hours. Sulfadiazine was continued until the eleventh day, February 2, when a rash developed, and the drug was stopped.

Despite excellent clinical improvement, the following cultures continued to be positive for *Candida*: blood cultures taken on January 30, February 1, throat cultures taken on February 5, urine cultures made on January 30 and February 7, and a stool culture made on February 4.

Sodium iodide was given intravenously on February 4 and then thymol 0.5 gm and syrup of hydriodic acid 4 c c t i d were started. Blood cultures on February 5 and February 7 were sterile. The patient was discharged on this therapy on February 7, the sixteenth hospital day.

In passing, it may be said that no growth of *Candida* was noted in blood cultures taken from other patients during the time our patient was in the hospital. A blood culture from one of the patient's neighbors on the ward was sterile on the day our patient's blood was positive.

On February 2 a culture of the fungus was sent to Dr C W Emmons of the U S Public Health Service, Bethesda, Maryland. He confirmed the diagnosis of *Candida* and identified it specifically as *Candida albicans*.

**Interval Note.** At home the patient continued to take iodides, and eventually returned to work, despite a slight cough. He visited the hospital clinic on February 20, at which time blood, throat and urine cultures were taken. Both throat and urine cultures still yielded *Candida albicans*, the blood culture was negative. At this time, too, the patient's wife submitted to blood and throat cultures, the latter of which yielded the same microorganism. A throat culture from the patient's daughter was also positive for *Candida albicans*.

**Second admission.** On May 16 the patient entered the hospital for further study. There were no complaints. Urine, blood examination, the Wassermann reaction and the blood non-protein nitrogen were all within normal limits. Stereoscopic views of the chest were negative. A stool on May 17 was positive for *Candida*. Cystoscopy May 18 revealed the entire bladder floor to be markedly thickened and edematous. Each ureter was catheterized and specimens from each were positive for *Candida*. Retrograde pyelograms were negative except for slight dilation of the left kidney pelvis and lower calyces. Culture of prostatic secretions was negative. Bronchoscopy May 20 failed to reveal ulceration or stenosis, though there was moderate edema throughout. Secretions were collected for cultural study, these were positive for *Candida* on June 5. The culture was subsequently suspended in saline and 1 c c inoculated intravenously into a rabbit. The animal died nine days later, many abscesses were found in the kidneys, and yeast was recovered culturally from the heart's blood and kidney of the animal. Following completion of this study the patient was discharged May 22.

A culture of *Candida albicans* isolated from the patient's blood in May was studied in October 1943 by Dr G L Hobby, of the Department of Medicine of Columbia University, with particular reference to the action of penicillin in vitro. Dr Hobby states that this culture is completely resistant to the action of penicillin, which agrees with the results which she has obtained previously with old stock cultures.

## COMMENTS

It seems likely that moniliasis of the respiratory tract existed for some years prior to the present illness, in view of the history of coughing spells, dyspnea and wheezing. A mild bronchial asthma, also present, may have been causally related to the fungus infection. Allergic phenomena following moniliasis have been reported by Castellani and others.

The significance of the urinary symptoms, also present for several years, is difficult to evaluate. However, the bladder lesions seen by cystoscopy appeared chronic and probably represented old lesions. If this assumption is correct, it is fair to postulate that in this patient protracted, low-grade hematogenous infection must have occurred, with filtering out of the fungi in the kidneys. Although no lesions could be demonstrated in the kidney, the inflammation in the bladder, coupled with positive ureteral cultures and sterile prostatic fluid, suggest renal moniliasis.

In January 1943 the patient developed a severe bronchitis which, though it responded to chemotherapy, sufficiently lowered his resistance to allow *Candida albicans* to spread through the blood stream. Whether the favorable clinical course was determined by the patient's resistive powers or by the low virulence of the organism is open to speculation. It must, however, be realized that slowly progressive lesions may still exist, which will only become apparent in time.

Apparently the sulfadiazine was effective only against the pyogenic cocci which were present in the respiratory tract. Though the iodides had no effect on the respiratory and urinary tract cultures, it is noteworthy that five blood cultures were positive for *Candida* before this therapy was instituted, but 24 hours later the blood became sterile and remained so throughout the subsequent course.

It is interesting to consider the significance of the presence of *Candida albicans* in the throats of the patient's wife and daughter. The former had a cough for six months which might have been indicative of pathological changes in the respiratory tract, although studies to establish such changes were not carried out. There is perhaps, some epidemiologic significance in the fact that the patient is employed in the New York Central freight yards at Selkirk, New York. Freight trains and their crews leave from this junction for destinations all over the continent. The possibility of this individual acting as a focus for the dissemination of a pathogenic fungus should be considered.

We can offer no adequate explanation for the rarity of positive blood cultures in cases of *Candida* infection. It is possible that more frequent culturing of the blood in cases of this sort would demonstrate that the finding is not actually rare.

## SUMMARY

This case represents an instance of systemic moniliasis due to *Candida albicans* in which cultures of the microorganism were obtained from the blood, bronchial secretions, pharynx and urine and feces. As far as we know it is the first case recorded in which *Candida albicans* has been demonstrated in the blood stream during life.

*Acknowledgment* We wish to express our thanks for their assistance in this study to the following: Dr C W Emmons, U S Public Health Service, Dr Arthur W Wright, Professor of Pathology and Bacteriology, of the Albany Medical College, Dr G L Hobby, of the Department of Medicine, Columbia University, and Dr L W Gorham, Professor of Medicine, of the Albany Medical College.

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- 3 WIKLER, A, WILLIAMS, E G, DOUGLASS, E D, EMMONS, C W, and DUNN, R C Mycotic endocarditis, Jr Am Med Assoc, 1942, cxix, 333-336
- 4 JOACHIM, H, and POLAYES, S H Subacute endocarditis and systemic mycosis (monilia), Jr Am Med Assoc, 1940, cxv, 205-208
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- 6 POLAYES, S H, and EMMONS, C W Final report on the identification of the organism of the previously reported case of subacute endocarditis and systemic mycosis (monilia), Jr Am Med Assoc, 1941, cxvii, 1533-1534
- 7 CASTELLANI, A Notes on certain bronchomycoses which may simulate pulmonary tuberculosis, Am Rev Tuberc, 1927, xvi, 541-574

## EDITORIAL

### *THE VIRUS OF LYMPHOGRANULOMA VENEREUM*

LYMPHOGRANULOMA venereum is a disease which presents itself in a number of different clinical types. The infection is usually transmitted by sexual contact, and the presenting lesions are generally located in the genital and perineal region. The indolent ulcerating inguinal buboes (climatic buboes, tropical buboes) commonly seen in men, esthiomène with hypertrophy and ulceration of the labia, and the ano-rectal syndrome with proctitis and rectal stricture, were all recognized and described as distinct clinical entities many years ago. That these were merely different manifestations of the same disease was not realized until Frei<sup>1</sup> in 1925 devised his intracutaneous test, utilizing as antigen pus aspirated from inguinal buboes.<sup>2</sup>

A major advance was accomplished when Hellestrom and Wassén<sup>3</sup> in 1930 succeeded in isolating the virus. They inoculated pus aspirated from inguinal buboes intracerebrally into monkeys, and produced a meningo-encephalitis in these animals. An antigen (like a Frei antigen) prepared from the brain tissues of such monkeys caused a positive intracutaneous reaction in human patients who reacted positively to the Frei test. This work has been repeatedly confirmed. The infection has been maintained by serial inoculations in monkeys and also in mice which are likewise highly susceptible to intracerebral inoculation. Lesions have also been produced less regularly by intracutaneous, intracorneal and intraperitoneal inoculations, and other laboratory animals can be infected, but the mouse appears to be the most satisfactory. By this method the virus has been obtained and identified from a variety of human lesions, including the small initial ulcer ("chancr"), the inguinal buboes, the labial tissue in esthiomene, the rectal mucosa, the urethra and cervix, from conjunctival exudates, and from the spinal fluid in cases with meningitis. This is the only procedure which furnishes conclusive proof of the nature of a suspected lesion.

Infection in man may occur by other routes, as through the skin (of the finger, with secondary involvement of the axillary lymph nodes), through the mouth, and probably the respiratory tract. The virus is not limited to the conspicuous local lesions, but it may become generally disseminated. The disease may run the course of an acute systemic infection, as in the cases of accidental infection of laboratory workers reported by Harrop.<sup>4</sup>

<sup>1</sup> FREI, W. Eine neue Hautreaktion bei Lymphogranuloma inguinale, *Klin Wchnschr*, 1925, iv, 2148.

<sup>2</sup> For an excellent general review, see KOTEEN, H. Lymphogranuloma venereum, *Medicine*, 1945, xxiv, 1-69.

<sup>3</sup> HELLESTROM, S., and WASSEN, E. Meningo-enzephalitische Veränderungen bei Affen nach intracerebraler Impfung mit Lymphogranuloma inguinale, *Verhandl 8te Internat Kongr Dermat u Syph*, 1930, 1147.

<sup>4</sup> HARROP, G. A., RAKE, G. W., and SHAFFER, M. F. New clinical conceptions of lymphogranuloma venereum, *Trans Assoc Am Phys*, 1941, lvi, 101.

Many other lesions have been attributed to this virus on the basis of a positive Frei test, or because of the production of a positive intracutaneous test with antigen prepared from suspected lesions, carried out on other individuals who give a positive Frei reaction. This procedure is often referred to as an "inverted Frei test." Its complete dependability as proof that a lesion is caused by the virus of lymphogranuloma inguinale is not as yet generally accepted.

The virus is filtrable through the filters usually employed, and according to Findley it is from 0.125 to 0.175 micron in diameter. Like other viruses it can not be cultivated on ordinary media, but grows only in living cells. It has been grown in tissue cultures and on the chorioallantoic membrane of an embryo chick. Rake et al.<sup>5</sup> found that it will grow luxuriantly in the yolk sac of the chick embryo, and this has proved a valuable method of obtaining uncontaminated virus in large quantities. This has largely replaced other materials in preparing virus for the Frei test. It has also provided favorable conditions for studying the morphology of the virus.

Several earlier observers described inclusion bodies in the cells of infected exudates, notably in monocytes, which they believed represented the virus. Findley et al.<sup>6</sup> described them in greater detail as seen in the brain cells of infected mice, and believed that they could trace a developmental cycle of the virus. Rake et al.<sup>7</sup> have confirmed this by a study of infected chick embryo yolk sacs. Following inoculation of the yolk sac, for some hours they were unable to detect virus microscopically except the elementary bodies contained in the inoculum. These were minute structures which took a reddish color with their differential stain and appeared to be about 0.4 micron in diameter. After about 12 hours, "initial bodies" were seen in small numbers inside the cells. They appeared first as isolated structures about 1 micron in diameter, near the cell membrane. Later they appeared in pairs, tetrads, and small groups. They stained a greenish color. The groups became segregated within small vesicles in the cell cytoplasm, surrounded by a limiting membrane (possibly a defense mechanism of the invaded cell) and embedded in a greenish staining matrix. These bodies increased in size up to a diameter of 4 to 7 micra, and then began to show differentiation in internal structure. Minute red-staining elementary bodies about 0.4 micron in diameter appeared, together with small vacuoles, from which the authors believed elementary bodies had escaped. The cell might then rupture, liberating the elementary bodies which then might enter into fresh cells and start another similar cycle of development, or the formation of elementary bodies might continue until the vesicle practically filled the entire cell. This

<sup>5</sup> RAKE, G., MCKEE, C. M., and SHAFFER, M. F. Agent of lymphogranuloma venereum in yolk sac of developing chick embryo, *Proc Soc Exper Biol and Med*, 1940, xliii, 332.

<sup>6</sup> FINDLEY, G. M., MACKENZIE, R. D., and MACCALLUM, F. O. A morphological study of the virus of lymphogranuloma inguinale (Climatic Bubo), *Trans Roy Trop Med and Hyg*, 1938, xxxii, 183.

<sup>7</sup> RAKE, G., and JONES, H. P. Studies on lymphogranuloma venereum. I. Development of the agent in the yolk sac of the chick embryo, *Jr Exper Med*, 1942, lxxv, 323.

process went on until at the death of the embryo substantially every cell of the yolk sac might be involved. The infective titer of the contents of the yolk sac rose in parallel with the observed increase in virus bodies.

This process as described by Rake resembles that reported in inclusion blennorrhoea and trachoma, and particularly the cycle in psittacosis as described in the spleen of infected mice by Bedson and Bland<sup>8</sup> and by many subsequent observers.

The virus of lymphogranuloma induces specific immune reactions in infected animals and human beings. The Frei test is a manifestation of a local immune or allergic reaction. This may become positive within a week after infection and usually does so within three weeks, but occasionally only after three months. In a small percentage of cases it fails to develop ("anergy"). Although the reliability of the test is questioned by some observers, the consensus of opinion is that if properly performed it has a high degree of specificity. An individual who has once given a positive reaction will usually continue to do so indefinitely. A few cases of reversion, however, have been reported after effective chemotherapy.

Along with cutaneous hypersensitiveness, antibodies appear in the serum. The most significant manifestation of this is the capacity of the serum specifically to neutralize the virus. This was demonstrated by Levaditi, and has been used by Findley and others to demonstrate the etiology of peculiar or unusual lesions. Complement fixation reactions may also be obtained. McKee and associates,<sup>9</sup> using as antigen virus obtained from the yolk sac of infected chick embryos, obtained positive reactions in a very large proportion of clinical cases of lymphogranuloma venereum. This seems to be at least as sensitive as the Frei reaction, and to be highly specific, although its dependability is not so thoroughly established. Harrop<sup>4</sup> regards a titer of 1-6 as diagnostic. A significant percentage of patients in venereal disease clinics, without clear clinical evidence of lymphogranuloma venereum, give positive complement fixation reactions and also often positive Frei reactions. There is good reason to believe that at least a large proportion of these are cases of latent infection with lymphogranuloma venereum virus.<sup>4</sup> None of these immune reactions, however, prove the nature of a presenting lesion. They merely indicate that the individual has at some time acquired the infection, and the current illness may be due to an entirely different agent.

Furthermore, the virus of lymphogranuloma venereum is related antigenically to that of psittacosis and to other viruses of the "psittacosis group," including trachoma, inclusion blennorrhoea, meningo-pneumonitis of Francis and Magill, and viruses obtained from certain cases of atypical pneumonia. All of these viruses and their specific antisera exhibit cross-reactions with one

<sup>8</sup> BEDSON, S. P., and BLAND, J. O. W. Developmental forms of psittacosis virus, *Brit. J. Exper. Path.*, 1934, xv, 243.

<sup>9</sup> MCKEE, C. M., RAKE, G., and SHAFFER, M. F. Complement-fixation test in lymphogranuloma venereum, *Proc. Soc. Exper. Biol. and Med.*, 1940, xlv, 410.

another in greater or less degree Levine et al<sup>10</sup> reported positive complement fixation reactions, using lymphogranuloma venereum antigen, in 11 cases of pneumonia caused by these viruses, although in the three cases showing the highest titer, the Frei reaction was negative Rake, however, has reported false positive Frei reactions in some cases of atypical pneumonia Clinically, the differentiation of these cases from lymphogranuloma venereum would usually be simple

Rake and Jones<sup>11</sup> have recently reported experiments which indicate the presence of a toxic agent in suspensions of lymphogranuloma venereum virus, and also of the related viruses of meningo-pneumonitis, mouse pneumonitis and feline pneumonitis After injections of relatively huge doses intravenously into mice, the animals died acutely, usually within four to 24 hours, and showed visceral lesions which they interpreted as the result of toxic degeneration rather than infection They regarded the toxic substance as analogous to bacterial endotoxins It was intimately associated with the elementary bodies in the suspensions It was very labile, and they were unable to render the virus noninfective without destroying the toxin By repeated injections into rabbits and chickens they obtained sera which neutralized a few mld of the toxin Serum from patients with lymphogranuloma venereum exerted a similar antitoxic action The antitoxic action of their immune sera, under the conditions of their experiments, was highly specific and limited to the homologous type of virus The sera did not show cross-reactions with other viruses of the group, noted with complement fixation and ordinary virus neutralization tests They suggested that this toxin neutralization may prove more useful in differentiating these closely related viruses than the serological procedures which have usually been employed

The virus of lymphogranuloma venereum differs from most other viruses in being in some degree susceptible to the sulfonamide drugs According to Rake et al<sup>12</sup> several other viruses of the psittacosis group are also susceptible to sulfonamides Their clinical value in the treatment of patients with lymphogranuloma venereum is generally recognized Sulfonamides will prevent the death of mice experimentally infected by intracerebral inoculation of this virus These animals, however, may present mild symptoms of infection Examination of the brain showed cellular infiltrations which might be substantially equal to those in untreated and fatally infected mice The brain tissue of such "cured" mice on inoculation into other mice or into chick embryos caused infection in them The sulfonamides, there-

<sup>10</sup> LEVINE, S, HILDER, E C, and BULLOVA, J G M Complement fixation for lymphogranuloma venereum and for psittacosis with Frei reaction among pneumonia patients, *Jr Immunol*, 1943, xlv, 183

<sup>11</sup> RAKE, G, and JONES, H P Studies on lymphogranuloma venereum II The association of specific toxins with agents of the lymphogranuloma-psittacosis group, *Jr Exper Med*, 1944, lxxix, 463

<sup>12</sup> RAKE, G, JONES, H P, and NIGG, C Sulfonamide chemotherapy of mouse pneumonitis, meningo-pneumonitis and lymphogranuloma venereum, *Proc Soc Exper Biol and Med*, 1942, xlix, 449

fore, exert a virostatic rather than a virocidal action. They suppress the clinical manifestations of infection and possibly induce a chronic carrier state, rather than effect a fundamental cure.

It seems likely that the same may be true in the case of human infection. The persistence of a positive Frei reaction in many treated cases suggests this. There is as yet no assurance that these cases are not infectious or that they may not relapse. Manifestly a great deal more study of these problems is needed.

In spite of many gaps in our knowledge, much has been accomplished toward clearing up the problem of lymphogranuloma venereum, with the isolation of the virus, its cultivation in the chick embryo, the development of reliable diagnostic procedures and the discovery of a reasonably effective therapy. This is of practical importance, since it is now known that the disease is relatively common among sexually promiscuous individuals, at least in the Southern States and on the Eastern Seaboard. These studies are also of theoretical interest in showing that the virus of lymphogranuloma venereum and the various viruses of the "psittacosis group" possess many distinctive features in common, which serve to separate them quite sharply from the other filterable viruses.



## REVIEWS

*Embryology of Behavior* By ARNOLD GESELL, M D 289 pages, 23.5 × 16 cm 1945 Harper & Brothers, New York Price, \$5.00

The author has compiled a number of very interesting observations "to indicate how an organic complexus of behavior is built up concomitantly with the bodily development of embryo, fetus and neonate" The observations are accompanied by extremely interesting photographic studies of the embryos One complete section of the book contains many chronological, behavior photographs titled, "A Photographic Delineation" Philosophical deductions, treatises and similar works are frequently cited, with especial favor being shown to Darwin, to substantiate various conclusions

Dr Gesell writes in his usual style, proving himself a worthy opponent of H L Mencken in word choice The subject matter is unique and interesting The photographs are clear and illustrative The book can be recommended for biologists, pediatricians and possibly obstetricians It has no use for parents other than those fully acquainted with medical terminology

J E B

## BOOKS RECEIVED

Books received during April are acknowledged in the following section As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them

*Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy* By JOHN A KOLMER, M S, M D, Dr P H, Sc D, LL D, L H D, F A C P 302 pages, 22 × 15 cm 1945 D Appleton-Century Company, New York Price, \$5.00

*The Examination of Reflexes A Simplification* By ROBERT WARTENBERG, M D Foreword by FOSTER KENNEDY, M D 222 pages, 18.5 × 12.5 cm 1945 The Year Book Publishers, Inc, Chicago Price, \$2.50

*Trauma in Internal Diseases With Consideration of Experimental Pathology and Medicolegal Aspects* By RUDOLF A STERN, M D Foreword by FRANCIS CARTER WOOD, M D 575 pages, 23.5 × 15.5 cm 1945 Grune & Stratton, Inc, New York Price, \$6.75

*Constitution and Disease Second Revised Edition Applied Constitutional Pathology* By JULIUS BAUER, M D 247 pages, 22 × 15 cm 1945 Grune & Stratton, Inc, New York Price, \$4.00

*Doctors at War* Edited by MORRIS FISHBEIN, M D 418 pages, 24 × 16.5 cm 1945 E P Dutton & Company, Inc, New York Price, \$5.00

*The New-Born Infant A Manual of Obstetrical Pediatrics* Third Edition, thoroughly revised By EMERSON L STONE, M D, 314 pages, 20.5 × 14 cm 1945 Lea & Febiger, Philadelphia Price, \$3.25

*Bronchial Asthma* By LEON UNGER, B S, M D, F A C P Introduction by MORRIS FISHBEIN, M D 724 pages, 25 × 16 cm 1945 Charles C Thomas, Springfield, Illinois Price, \$9.00

*The Rockefeller Foundation A Review for 1944* By RAYMOND B FOSDICK, President of the Foundation 63 pages, 23 × 15.5 cm 1945 The Rockefeller Foundation, New York

# COLLEGE NEWS NOTES

## ENLISTMENTS AND DISCHARGES, A C P MEMBERS

Dr Alexander McCausland (Associate), Blacksburg, Va, has been commissioned a Lieutenant (j g) in the U S Navy This brings the total number of College members who have entered upon military duty to 1,858

The following members of the College have been honorably discharged

William R Galbreath, Major, (MC), AUS—New Orleans, La  
Wendell Charles Hall, Major, (MC), AUS—Hartford, Conn  
Lorenzo Dow Massey, Major, (MC), AUS—Osceola, Ark  
Paul R Meyer, Captain, Army Air Corps—Port Arthur, Tex

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## ORAL EXAMINATIONS AMERICAN BOARD OF INTERNAL MEDICINE

Oral examinations by the American Board of Internal Medicine were held at New Orleans, May 21-22-23, at Philadelphia, June 6-7-8 They will be held in Chicago, June 27-28-29 and in San Francisco, October 15-16-17 The examinations at San Francisco are intended for candidates from Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming The closing date for registering for the San Francisco examination is September 1

Write for application form to the American Board of Internal Medicine, 1301 University Ave, Madison 5, Wisconsin

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## GIFTS TO THE COLLEGE LIBRARY

The following gifts of publications by members are gratefully acknowledged

### *Books*

John A Kolmer, F A C P, Philadelphia, Pa—an autographed copy, "Penicillin Therapy," D Appleton-Century Company  
Franklin B Peck, F A C P, Indianapolis, Ind—a bound volume, No 3, 1944 complete, "Diabetes Abstracts"  
Benjamin Saslow, F A C P, Newark, N J—"Manual of the Diabetic Clinic," Presbyterian Hospital of Newark  
Peter J Steincrohn, F A C P, Hartford, Conn—"Forget Your Age"

Also acknowledged is a gift from the National Research Council, Division of Medical Sciences, "Primate Malaria"

### *Reprints*

M Meredith Baumgartner, F A C P, Lieutenant Commander, (MC), USNR—1 reprint  
C Wesley Eisele, F A C P, Chicago, Ill —1 reprint  
Cecil M Jack, F A C P, Decatur, Ill —1 reprint  
Harry Parks (Associate), Atlanta, Ga —1 reprint  
Frank B Queen, F A C P, Lieutenant Colonel, (MC), AUS—1 reprint  
Milford O Rouse, F A C P, Dallas, Tex —2 reprints

Sidney Scherlis (Associate), Captain, (MC), AUS—1 reprint

Bernard M Scholder, F A C P, Lieutenant Commander, (MC), USNR—1 reprint

James S Sweeney, F A C P, Colonel, (MC), AUS—1 reprint

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#### CAPTAIN JAMES GRAHAM BRUCE, (MC), AUS LIBERATED FROM BATAAN

Captain James Graham Bruce, (MC), AUS was among three members of the American College of Physicians who were rescued at Manila during General MacArthur's invasion of the Philippines. The other two were Lieutenant Commander William M Siliphant, (MC), USN, and Lieutenant Commander J La Monte Zundell, (MC), USN.

Temporarily, Captain Bruce's address is 24 Hooker Ave, Poughkeepsie, N Y. After his medical survey at the Lovell General Hospital, Fort Devens, Mass, we understand he will be given a leave of absence and will then be assigned to special work in internal medicine.

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#### LIEUTENANT M LEONARD GOTTLIEB, A PRISONER IN JAPAN

Lieutenant M Leonard Gottlieb, (MC), USNR, an Associate of the College, has been a prisoner of the Japanese since the early part of the war. Word has been received that he has been transferred from the Zentsuji War Prison Camp to Camp Shinagawa in Tokyo. The last direct word from Lieutenant Gottlieb was written during December, 1943, arriving here in February, 1945. His earlier letter stated that the Japanese had given the American doctors some medical books and allowed them to form a medical society of American and British physicians, and permitted them to have some scientific conferences.

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#### REPORT FROM THE OFFICE OF THE SURGEON GENERAL, U S ARMY

The 5th Annual Meeting of the Army Epidemiological Board was held April 26-27 at the Office of The Surgeon General. The meeting was presided over by Dr Francis G Blake, F A C P, Dean of Yale University School of Medicine, New Haven, Conn, who is Civilian Consultant to the Secretary of War and President of the Board.

The Epidemiological Board is administered by the Preventive Medicine Service, Office of The Surgeon General. It consists of a Central Board and ten Commissions on Acute Respiratory Diseases, Air-Borne Infections, Epidemiological Survey, Hemolytic Streptococcal Infections, Influenza, Measles and Mumps, Meningococcal Meningitis, Neurotropic Virus Diseases, Pneumonia, and Tropical Diseases. The work of these Commissions, however, is not limited to the field indicated by the name, but is authorized according to opportunities, facilities and specialties of members.

During the past year extensive epidemiological investigations have been conducted in this country and in several theaters of operations overseas. This work has not only proved of practical value to the Army, but has materially increased the fundamental scientific knowledge of the causes and control of infectious diseases among the civilian as well as the military population.

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Major General Merritte W Ireland, F A C P, USA, Retired, who modernized the Army Medical Department when he became Surgeon General after World War I, recently received a citation from the Medical Society of the District of Columbia for distinguished services to humanity and military medicine.

The ceremony was attended by the present Surgeon General of the Army, Major General Norman T. Kirk, F A C P, distinguished medical officers from the Army, Navy and Public Health Service, and other prominent physicians and scientists.

General Ireland, who was born 78 years ago in Columbia City, Ind., was graduated from the Detroit College of Medicine and Surgery in 1890, served as Chief Surgeon of the AEF in France during World War I, and as Surgeon General of the U S Army from 1918 to 1931. Previous honors accorded him include the William Freeman Snow Medal, the U S Distinguished Service Medal, Companion of the Order of the Bath (Great Britain), Commander of the Legion of Honor (France), the Serbian Red Cross Silver Medal and the Polish Polonia Restituta.

Brigadier General Hugh J. Morgan, F A C P, Director of the Medical Consultants Division, Office of The Surgeon General, recently returned from overseas after ten weeks of duty in the European and Mediterranean theaters of operations where he has been inspecting medical installations and conferring on medical problems pertinent to those theaters.

Colonel William C. Menninger, F A C P, Chief Consultant in Neuropsychiatry to The Surgeon General, presided at a conference of Service Command Consultants in Neuropsychiatry at The Surgeon General's Office, April 20-21.

General subjects on the program included induction centers, hospitalization problems, reconditioning, clinical psychology, psychiatric social workers and assistants, mental hygiene consultation services, neurology, disciplinary barracks and rehabilitation centers, school of military neuropsychiatry, preventive psychiatry, personnel, nomenclature, redeployment, history, and public relations.

Among Consultants in Neuropsychiatry in the Army are Lieutenant Colonel Clarke H. Barnacle, F A C P, Seventh Service Command, Colonel Franklin G. Ebaugh, F A C P, Eighth Service Command, and Lieutenant Colonel Lauren H. Smith, F A C P, Ninth Service Command. Dr. Edward A. Strecker, F A C P, Philadelphia, Pa., is one of the Civilian Consultants to The Surgeon General.

Colonel Irving S. Wright, F A C P, has been transferred as Consultant in Medicine from the Sixth Service Command to the Ninth Service Command, Colonel Alexander Marble, F A C P, former Chief of Medical Service, Harmon General Hospital, is now Medical Consultant, Sixth Service Command, Lieutenant Colonel Worth B. Daniels, F A C P, is now Chief of Medical Service at Harmon General Hospital, Longview, Tex.

Lieutenant Colonel Burgess L. Gordon, F A C P, has been appointed Chief of the Medical Service at the new Army General Hospital at Camp Pickett, Va. He was formerly Assistant to the Chief of the Administration branch, Hospital Division, Office of The Surgeon General.

The Harmon General Hospital has been designated for the treatment of tropical diseases. The only other such Army center is the Moore General Hospital at Swananoa, N C. Colonel G. V. Emerson, F A C P, is the Commanding Officer.

#### *Educational Opportunities for Army Doctors*

Since the start of World War II, over 6,000 selected medical officers have been graduated from short but intensive courses given by the Medical Department in some thirty critical medical and surgical specialties, according to Major General George F.

Lull, F A C P, Deputy Surgeon General. In addition, refresher courses in general medicine and surgery provide medical officers with a chance to "brush up" before returning to professional assignments after other duty

Many doctors also benefit while in service from working under key professional personnel in military hospitals. Other medical officers who have been on duty with combat troops in the field are given an opportunity to brush up on their specialty through the rotation policy.

General Lull reported that 350 doctors have been reassigned from field to hospital duty during the past year in the Mediterranean Theater and "the merit of intra-theater rotational plans has been pointed out to other theaters, and is being encouraged in order that the maximum number of doctors might receive refresher training while they are still in military service."

Naturally, professional training of medical corps officers during military service must be restricted to meet military rather than civilian requirements. However, General Lull said The Surgeon General is keenly interested in the welfare of these doctors and will provide "insofar as is possible" opportunities for professional training.

In the post-war period, he added, all doctors will be entitled to professional training, after their release from service, under the G I Bill of Rights, and those who remain in the Army will have the opportunity for refresher training at selected military hospitals and civilian schools.

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### *Promotions in the Army Medical Corps*

#### From Colonel to Brigadier General

George R. Callender, F A C P, Everett, Mass  
W. Lee Hart, F A C P, York, S. C.

#### From Lieutenant Colonel to Colonel

Eugene Charles Eppinger (Associate), Brookline, Mass  
Edwin Gabriel Faber, F A C P, Tyler, Tex  
Edwin Matthew Goyette (Associate), Burlington, Vt  
William Donald Graham (Associate), St. Paul, Minn  
Gilbert Henry Marquardt, F A C P, Chicago, Ill  
Johnson McGuire, F A C P, Cincinnati, Ohio  
Carl Alfred Schuck (Associate), St. Louis, Mo  
Joseph Bedford Vander Veer (Associate), Philadelphia, Pa

#### From Major to Lieutenant Colonel

Maurice James Abrams, F A C P, Brewton, Ala  
Eric MacMillan Chew, F A C P, Mercer Island, Wash  
Adam James French (Associate), Ann Arbor, Mich  
Edward Alfred Greco, F A C P, Portland, Maine  
Paul Victor Hamilton, F A C P, Cincinnati, Ohio  
Hugh Edward Kiene (Associate), Providence, R. I.  
Frederick Lemere, F A C P, Seattle, Wash  
Thomas Wilson Martin (Associate), Pittsburgh, Pa  
Theodore John Pfeffer, F A C P, Racine, Wis  
Herbert William Rathe, F A C P, Waverly, Iowa  
Kenneth McLane Smith (Associate), Columbus, Ohio  
Walter Maximilian Solomon, F A C P, Shaker Heights, Ohio  
Joseph Blackburn Stevens (Associate), Greensboro, N. C.

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DR JOSEPH S EVANS, ACTING GOVERNOR FOR WISCONSIN

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Dr Joseph S Evans, F A C P, Professor of Medicine at the University of Wisconsin, has been appointed the Acting Governor of the College for Wisconsin during the absence of Dr Elmer L Sevringhaus while on a mission to Italy

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Lieutenant Colonel Zacharias Bercovitz, F A C P, formerly of New York City, is now Chief of the Medical Service of a large Army hospital in Assam, India

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Colonel Benjamin J Birk, (MC), AUS, Milwaukee, Wis, is now on duty in China He was recently awarded the Legion of Merit Medal "for exceptionally meritorious conduct in the performance of outstanding services" For a period of time, Colonel Birk was commanding officer of a hospital troop ship He then went to India in February, 1944, and in April of that year was flown over the Himalayan "Hump" to China and has served as medical officer with an American liaison group attached to Chinese combat forces in the fighting about Kweilin, Changsha, Hengyang, Chaun Shien and Luichow

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Lieutenant Commander George F Schmitt, Jr, F A C P, formerly of Rochester, Minn, and now serving in the U S Naval Reserve, has compiled a diet formulary which has been printed and circulated by the Navy's medical department The formulary is condensed in 102 pages and includes diets, caloric contents of various foods, heights-weights table for men and women and other information concerning diets

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Major John B Levan, F A C P, formerly of Reading, Pa, has been Chief of the Cardiovascular Section at the McCloskey General Hospital (4,000 bed capacity) since September, 1942

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Dr Robert S Berghoff, F A C P, President-Elect of the Illinois State Medical Society, was recently elected President of the Staff of Mercy Hospital, Chicago Mercy Hospital is the oldest hospital in Illinois, established in 1850, ninety-five years ago

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DR J C GEIGER AGAIN DECORATED

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His Royal Majesty, Haakon, The King of Norway, has conferred upon Dr J C Geiger, F A C P, San Francisco, through the Minister of Foreign Affairs of Norway, the Right Honorable Trygve Halvdan Lie, head of the Norway Delegation at the UNCIO Conference, the Order of St Olaf, First Class This order was established in 1847 by Oscar, 1st, in honor of St Olaf, the founder of Christianity in Norway The decoration carries with it an Honorary Knighthood and the following citation "For valuable and distinguished service to Norway in World War II, and for unswerving devotion and intelligent administration of public health in order that human lives be preserved and the world made a better and happier place to live"

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Dr Kendall A Elsom, F A C P, now Lieutenant Colonel, (MC), AUS, is Chief of Medical Service at the Fort Benning Regional Hospital, Ga

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The Southeastern Regional Medical Conference of the Army Air Forces was held April 23-24 at the AAF Tactical Center, Orlando, Fla Chairmen at the

various sessions included Lieutenant Colonel Harold F Robertson, F A C P, Lieutenant Colonel J F Panton, F A C P, and Lieutenant Colonel Albert W Wallace, F A C P

Among members of the College participating on the scientific program were

Colonel Donald D Flickinger (Associate), "Medical Experiences in C B I Theater of Operations",

Dr Francis F Borzell, F A C P, Chairman of the War-Time Graduate Medical Meetings Committee, Philadelphia, "Relation of Roentgenology to Internal Medicine",

Colonel W Paul Holbrook, F A C P, Office of the An Surgeon, Washington, and Major Arie van Ravenswaay (Associate), "Recent Epidemic of Type 17 Sulfonamide Resistant Hemolytic Streptococci",

Lieutenant Colonel Harold F Robertson, F A C P, et al, "Early Physical Activity During Acute Rheumatic Fever",

Lieutenant Colonel Albert W Wallace, F A C P, "Streptococcus Pneumonia",

Dr Simon S Leopold, F A C P, Philadelphia, "Chest Pains",

Lieutenant Colonel J F Panton, F A C P, "The Electrocardiographic Findings in Primary Atypical Pneumonia",

Captain William M Sheppe, F A C P, (MC), USNR, "Primary Atypical Pneumonia and Its Complications",

Dr James S McLester, F A C P, Birmingham, "Diseases of Nutrition",

Lieutenant Colonel Paul K French, F A C P, "Infectious Mononucleosis",

Lieutenant Colonel Robert J Needles, F A C P, "Peptic Ulcer versus Functional Indigestion"

#### A C P REGIONAL MEETING HELD AT BUFFALO, MAY 12

Under the Governorship of Dr Nelson G Russell of Buffalo and the able assistance of Dr Roy L Scott, F A C P, Chairman of Arrangements, a limited regional meeting of the College for Western New York was conducted at Buffalo on May 12. As guests, Fellows of the College from Ontario were invited and several were in attendance.

The morning session was held at the New York State Institute for the Study of Malignant Diseases. Dr W H Wehr and his associates presented the program and conducted the group through the Pathological and X-ray Departments.

Luncheon was served in the solarium of the Buffalo General Hospital, after which the following program was given:

"Observations in Neurocirculatory Asthenia"—Mandel E Cohen, M D, Boston,

"Vitamin Deficiency in Tuberculosis"—David K Miller, M D, Buffalo,

"Acute Diarrheal Diseases: A Note on Effect of Streptomycin in Typhoid Fever"—Hobart A Reimann, M D, F A C P, Philadelphia,

"Somatic Pain—Diagnostic and Therapeutic Aspects of Local Infiltration"—Bernard D Judovich, M D, Philadelphia,

"Treatment of Hyperthyroidism with Thiouracil"—George F Koepf, M D, Buffalo

In the evening a reception and dinner were held at the Saturn Club. Mr Edward R Loveland, Executive Secretary of the College, addressed the dinner meeting on the "Activities and Objectives of the College and Its Plans for the Immediate Future."

The scientific program was noteworthy and the attendance was exceedingly good—the great majority of the members of the College from the western half of New York were in attendance.

## GOVERNMENT BUILDING NEW HOSPITAL, GEORGE WASHINGTON UNIVERSITY

Announcement was recently made that Dr Walter A Bloedorn, F A C P , Dean of George Washington University School of Medicine, has been appointed Medical Director of the new George Washington University Hospital, which is being built by the federal government for the use of the University to meet the needs of the war-time emergency in Washington. The new hospital will have a capacity of 400 beds and will be equipped and managed as a teaching hospital

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U S PHARMACOPEIAL CONVENTION ACQUIRES NEW HEADQUARTERS  
IN PHILADELPHIA

The Board of Trustees of the U S Pharmacopeial Convention has recently purchased temporary headquarters at 4738 Kingsessing Ave , Philadelphia. Heretofore the Pharmacopeial Revision Chairman has maintained quarters in the building of the Philadelphia College of Pharmacy and Science, but the increasing volume of work has necessitated larger accommodations

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GOVERNOR DEWEY, NEW YORK, VETOES BILLS RECOGNIZING UNACCEPTED  
MEDICAL SCHOOLS

Governor Dewey of New York recently vetoed two bills which had been passed by the New York Legislature permitting the granting of medical license to graduates of any medical school in the United States. If these bills had been permitted to stand, it is believed that diploma mills and all sorts of substandard schools of medicine would have been revived and all that has been accomplished in the past years in maintaining high standards of recognized medical schools would have been temporarily lost

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Commander Thomas D Martin, F A C P , (MC), USNR, formerly of Tampa, Fla , received the following citation, as recommended by Admiral C W Nimitz recently "For meritorious and efficient performance of duty as chief of medical service at a fleet hospital in the South Pacific area from May 21, 1943 to March 25, 1944. During this period Commander Martin displayed exceptional professional skill in handling the many medical problems which arose. Through his organizational ability and thorough indoctrination of the medical officers and nurses under his supervision he contributed materially to the efficient administration of the hospital to which he was attached. His initiative and leadership were in keeping with the highest traditions of the naval service"

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Dr David P Barr, F A C P , New York, acted as Chairman of a Symposium on Peptic Ulcer before a regional meeting of the American Society for Research on Psychosomatic Problems on May 11

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The University of Texas Medical Branch, Galveston, recently announced the founding of a research fellowship in internal medicine in honor of Dr Marvin Lee Graves, F A C P , Emeritus Professor of Internal Medicine. Funds were donated by Dr Graves' children in his honor. The fellowship will be filled annually by the Department of Medicine "through the appointment of a graduate in medicine who is considered most likely to maintain the professional standards and ideals of Dr Graves," according to the announcement



Dr George M Decherd, Jr, F A C P, Associate Professor of Internal Medicine at the University of Texas Medical Branch, Galveston, will direct a new postgraduate medical training program there. It is proposed that the program will embody short postgraduate conferences and courses on special subjects, two-day conferences given by the faculty in cooperation with county and district medical societies over the state, and residency training for specialty board certification and specialty practice.

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The Commonwealth Fund has appropriated \$8,200 to be used by Dr Carl J Wiggers and associates of the Department of Physiology for continuance of their studies on the peripheral circulation and shock during 1945-46.

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Dr Lawrence Parsons, F A C P, of Reno, Nevada, addressed (by invitation) the Sacramento Society for Medical Improvement (Sacramento, California, County Medical Society) on April 17, 1945. He spoke on Relapsing Fever at Lake Tahoe, California-Nevada. Lantetn slides of photomicrographs of blood films showing the causative organism, *Borrelia recurrentis* and specimens of the tick transmitters, *Omnithodorus hermsi* and *O parkeri* were presented. Lake Tahoe is an important endemic focus of relapsing fever in California since, in normal times, large numbers of visitors from all parts of the United States go there, occasionally contract the disease and often prove to be perplexing diagnostic problems upon their return home, particularly in the East.

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During the last three years, diphtheria has broken all bounds in Northern and Central Europe and thus become the leading epidemic disease, according to the Epidemiological Information Bulletin No 4 issued by UNRRA's Health Division. Fifteen years ago diphtheria was at about the same level all over Europe. Up to 1940 it was steadily reduced in most countries, but in Germany it began to increase. From 49,000 cases in 1927 the number of cases reported in the original territory of the Reich increased to 238,400 in 1943. In Norway, on the contrary, there were only 17 cases during the last six months before the German invasion.

The reduction of diphtheria among most of Germany's small neighbors had been brought about without systematic immunization, and the population was therefore not properly protected. This situation was all the more dangerous since a virulent type of diphtheria, not yielding to serum treatment, had spread in Germany. From 35 per cent in 1938 the proportion of fatal cases rose to over 6 per cent in 1943. Cases among adults became frequent, and diphtheria appeared in the German army even as a fatal complication of chest wounds.

With the invasion came diphtheria carriers, and explosive epidemics soon appeared in Norway, the Netherlands, Belgium, northern France and Czechoslovakia. In the course of the three last years, there have been nearly 50,000 cases in Norway, and about 150,000 cases in the Netherlands, which has three times the population of Norway. In the Netherlands, death from diphtheria now runs barely behind the mortality from tuberculosis in spite of the increase of the latter disease. Only Great Britain and Hungary, where immunization had been pushed to the limit, experienced no rise whatever.

It is pointed out that even oceans constitute no effective barrier against a carrier disease like diphtheria. The lesson drawn is that immunization can be safely relaxed only when diphtheria has been eradicated.

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The New York Rheumatism Association held its annual meeting at the New York Academy of Medicine, May 9, under the presidency of Dr Russell L Cecil, F A C P.

Among the speakers were Dr John Lansbury, F A C P, Philadelphia, "Dietary Deficiency in the Etiology of Interstitial Calcinosis", Dr Eugene F Trout, F A C P, Chicago, "Bone Marrow Findings in Arthritis", Lt Col Philip S Hench, F A C P and Major Edward W Boland (Associate), "Rheumatic Centers of the U S Army", Dr Abraham S Gordon, F A C P, Brooklyn, "Transmission of Gold Salts to the Fetus through the Placenta", and Capt Joseph L Hollander (Associate), et al, "Acute Arthritis Resembling Reiter's Syndrome"

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Dr George B Dorff, F A C P, Brooklyn, recently received a special citation for his work with the Selective Service of Brooklyn Dr Dorff is the retiring president of the East New York Medical Society

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Under the presidency of Elihu S Wing, F A C P, Providence, Rhode Island, the Rhode Island Medical Society held its 134th Annual Session of May 16-17 Dr Wing's presidential address was entitled, "Medical Care in Rhode Island"

Among guest speakers on the program were Dr Stanley P Reimann, F A C P, Philadelphia, Dr Roger I Lee, F A C P, Dr Elliott P Joslin, F A C P, and Dr Samuel A Levine, F A C P, the latter three of Boston

Dr Francis G Blake, F A C P, dean and Sterling professor of Medicine at Yale University School of Medicine, delivered the Chapin Oration on "Some Recent Advances in the Control of Infectious Diseases"

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Dr Josiah J Moore, F A C P, president of the Chicago Medical Society and treasurer of the American Medical Association, delivered the commencement address of the Montana State University, Missoula, earlier this month, and was awarded the honorary degree of Doctor of Laws Dr Moore is an alumnus of this institution

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Col Thomas T Mackie, F A C P, (MC), AUS, has been reelected president of the American Foundation for Tropical Medicine The Foundation received during 1944, \$47,350 from various sources toward its work Of this total, \$38,760 have been given in eleven grants to medical schools and other institutions for teaching and research purposes

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#### A C P POSTGRADUATE COURSES, AUTUMN 1945

The Executive Offices of the College and the Committee on Postgraduate Courses have been engaged in formulating a program of Postgraduate and Refresher Courses for the autumn of 1945, but much work is involved before all courses can be definitely announced

The following is the tentative program, although specific dates cannot yet be announced—it is expected that these courses will be given between the end of September and December 15

##### 1 Cardiology

One course of one week, November 5-10, under Dr Paul D White, Director, Massachusetts General Hospital and Harvard University, this is a repetition of Dr White's course given during the autumn of 1944, and is given primarily for those members of the College who were unable to obtain admission to the previous course This course already has applications on file practically to its capacity No non-members can be accommodated

One course in Advanced Cardiology for a more limited group is under consideration, and two different institutions and directors have been approached, final report will be published later

## 2 Alleigy

A one week course in Alleigy, probably during October, will be given by Dr Robert A Cooke, Director, at the Roosevelt Hospital, New York City, this will be essentially a repetition of Dr Cooke's course given for the College during the autumn of 1944

## 3 General Medicine

A one week's course by Dr Homer P Rush, Director, University of Oregon Medical School, essentially a repetition of Dr Rush's course given during the autumn of 1944

## 4 Internal Medicine

One or two courses planned, each of two weeks' duration, under consideration are courses at the University of Michigan Medical School, Northwestern University Medical School, and the University of Texas Medical Branch. Announcements will be made later

Other requests for courses, under consideration, include

### Endocrinology

Under Dr Willard O Thompson, Director, Chicago

### Gastro-enterology or Internal Medicine

Under Dr Walter L Palmer, Director, Chicago

### Physiology of Disease

### Tropical Medicine

### Metabolic Diseases

### Nutrition

Members of the College are requested to send in their suggestions and recommendations to the Executive Secretary of the College, Mr E R Loveland, 4200 Pine Street, Philadelphia 4, Pa

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## COMMITTEE ON POSTWAR MEDICAL SERVICE

The Joint Committee on Postwar Medical Service meets monthly in Chicago. Representatives on the Joint Committee come from the American Medical Association, the American College of Physicians, the American College of Surgeons, and many other interested organizations

The full minutes of these meetings are published in The Journal of the American Medical Association, and therefore are not repeated in the ANNALS OF INTERNAL MEDICINE

Minutes of the meeting held at Chicago on March 17 are the last available when this copy goes to press. Of particular importance was the report of Lt Col Lueth on the replies to questionnaires that had been distributed to medical officers. Forty-seven per cent have indicated that they desire to return to practice in their former communities after the war, more than 21 per cent indicated they do not plan to re-engage in practice in their former communities. Less than half of this latter group, however, gave a definite locality in which they would like to practice after the war

Lt Col Lueth made an extensive report on the analysis of those interested in Industrial Medical Practice and of Economic Aspects of Postwar Practice. His report is published in The Journal of the American Medical Association, issue of May 12, 1945, page 138.

Other items under discussion included Report on Educational Internship and Residency Opportunities for Medical Officers, activities of the Bureau of Information, a clearing bureau for all sorts of information to medical officers, Local Organization of Courses for Graduate Study, Report of the Subcommittee to Draw Up Recommendations to the Governors of the States (the draft of a letter was approved, placing the facilities of the Committee on Postwar Medical Service at the disposal of the Governors of the States, and making certain helpful suggestions concerning the provisions of Public Law 346, 78th Congress—the G I Bill of Rights—as they may affect the entire field of medical education, the Governor of each State is vested with the power and duty of certifying to the Veterans' Administration the institutions in his state which are qualified to give acceptable courses of education and training in each of many categories), Progress Report of Subcommittee on Surplus Medical and Hospital Supplies, Progress Report on Laws concerning Temporary Licensure, Formulation of Lists of Medical Officers to be Considered for Demobilization, Report of Subcommittee on Establishment of Medical Corps in the Veterans' Administration, Report of Subcommittee on Enrollment of Medical Students, and Informational Reports.

A meeting of the Joint Committee was held at Chicago on May 12, minutes of which will be published as soon as available.

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#### WAR-TIME GRADUATE MEDICAL MEETINGS

The activities of the War-Time Graduate Medical Meetings, of which the American College of Physicians is co-sponsor, have been prosecuted with increasing vigor in many sections during the first four months of the current year. This is gratifying in view of the restrictions of medical meetings generally caused by the regulation of the Office of Defense Transportation. The Surgeons General and the Office of Defense Transportation have recognized the valuable function performed by these meetings and consequently have been very liberal in their granting privileges of convention.

The Central Committee is hopeful that the civilian physicians will continue their cooperative support. It is recognized that the continuation of the war is producing increasingly greater strain on civilian physicians. While this activity is entirely a voluntary effort, we hope that none of us will become weary in well doing. Any information or opinions concerning the stimulation of activities of the War-Time Graduate Medical Meetings will be appreciated by the Central Committee.

GEORGE MORRIS PIERSOL, M D (American College of Physicians)

ALFRED BLALOCK, M D (American College of Surgeons)

F F BORZELL, M D (American Medical Association), Chairman

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#### WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr J A Lyon, Chairman, Dr C R Edwards, Dr C B Conklin

*A A F Regional Hospital Langley Field, Virginia*

June 29 Gastro-enterology—Dr Lay Martin

Traumatic Surgery of the Abdomen—Lieutenant R C Wood

*Newton D Baker General Hospital, Martinsburg, West Virginia*

June 18 Live! Diseases Seen in the Present War—Colonel Balduin Lucke

REGION No 14 (Indiana, Illinois, Wisconsin)—Dr W O Thompson, Chairman,  
Dr N C Gilbert, Dr W H Cole, Dr W D Gatch, Dr R M Moore, Dr H M  
Baker, Dr E R Schmidt, Dr E L Sevringhaus, Dr F D Murphy

*Gardner General Hospital, Chicago, Illinois*

June 20 Chest Diseases and Diseases of the Larynx

June 27 Low Back Pain

July 11 Heart Disease and Allied Conditions

July 18 Bone and Joint Infections

July 25 Arterial Vascular Disease—Traumatic Lesions

*Station Hospital, Fort Sheridan, Illinois*

June 20 Heart Disease and Allied Conditions

June 27 Bone and Joint Infections

July 11 Arterial Vascular Disease—Traumatic Lesions

July 18 Repair of Bone in Fractures and Diseases

July 25 Diseases of the Kidneys—Urogenital Tract

*Mayo General Hospital, Galesburg, Illinois*

June 20 Arterial Vascular Disease—Traumatic Lesions

June 27 Repair of Bone in Fractures and Diseases

July 11 Diseases of the Kidneys—Urogenital Tract

July 18 Blood Dyscrasias—Malaria—Filariasis

July 25 High Blood Pressure

*Vaughan General Hospital, Hines, Illinois*

June 20 Diseases of the Kidneys—Urogenital Tract

June 27 Blood Dyscrasias, Malaria, Filariasis

July 11 High Blood Pressure

July 18 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment

July 25 Conditions Affecting Glucose Metabolism

*Station Hospital, Camp Ellis, Illinois*

June 20 High Blood Pressure

June 27 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment

July 11 Conditions Affecting Glucose Metabolism

July 18 Brain and Spinal Cord Injuries

July 25 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care

*Station Hospital, Camp McCoy, Wisconsin*

June 20 Conditions Affecting Glucose Metabolism

June 27 Brain and Spinal Cord Injuries

July 11 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care

July 18 Plexus and Peripheral Nerve Injuries

July 25 Dermatological Diseases

*Station Hospital, Tular Field, Wisconsin*

- June 20 Dermatological Diseases
- June 27 Burns and Plastic Surgery
- July 11 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment
- July 18 Endocrinology
- July 25 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment

*Station Hospital, Chanute Field, Illinois*

- June 20 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment
- June 27 Psychosomatic Medicine
- July 11 Wound Healing and Tendon Surgery
- July 18 Mental Hygiene and the Prevention of Neuroses in War
- July 25 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases

*Billings General Hospital, Indiana*

- June 20 Wound Healing and Tendon Surgery
- June 27 Mental Hygiene and the Prevention of Neuroses in War
- July 11 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases
- July 18 Peptic Ulcer, Gall Bladder and Liver Diseases
- July 25 Low Back Pain

*Wakeman General Hospital, Indiana*

- June 20 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases
- June 27 Peptic Ulcer, Gall Bladder and Liver Diseases
- July 11 Low Back Pain
- July 18 Chest Diseases and Diseases of the Larynx
- July 25 Bone and Joint Infections

REGION No 23 (Nevada, Northern California)—Dr S R Mettler, Chairman, Dr E H Falconer, Dr D N Richards

*U S Naval Hospital, Mare Island, California*

- June 15 The Surgical Approaches to the Knee Joint—Dr LeRoy C Abbott

*Station Hospital, Fort Ord, California*

- June 16 Abdominal Surgery—Dr Thomas F Mullen
- June 23 Injuries to the Knee Joint—Dr Frederic C Bost

*Station Hospital, Camp Roberts, California*

- June 16 Severe Infections of the Hand—Dr Edmond D Butler
- June 23 Experiences with Infectious Diseases in Army Camps in England—Dr Gordon E Hein

*Station Hospital, Stockton Army Air Base, California*

- June 20 Diagnosis and Treatment of Arthritis—Dr Hans Wayne
- June 27 Injuries to the Knee Joint—Dr Carl E Anderson

Dr Willard O Thompson, F A C P, Chairman of Regional Committee No 14 of the War-Time Graduate Medical Meetings, was presented with the following Citation for distinguished service to the Sixth Service Command by Major General Reynolds, Commanding General

"In 1942 the American Medical Association, in conjunction with the American College of Surgeons and the American College of Physicians, established a fund to provide postgraduate medical instruction for medical officers stationed throughout the Army

"Dr Willard O Thompson, Chairman of the Committee for War-Time Graduate Medical Meetings for Region No 14 which includes Illinois and Wisconsin, obtained the services of prominent teachers and practitioners of medicine to lecture and conduct clinical exercises in the hospitals of the Sixth Service Command. He himself has actively participated in the teaching and by his boundless energy and enthusiasm has maintained the continuity and high quality of the program. The medical officers of this Service Command as well as hundreds of civilian physicians who have attended the courses at Army hospitals have universally expressed their appreciation for this unusual opportunity for postgraduate instruction which has definitely raised the standard of medical practice in the Sixth Service Command

"Dr Thompson, as Chairman of the Committee, by his untiring efforts and devotion to this important program, has rendered distinguished service to the Sixth Service Command and in recognition thereof the Commanding General is pleased to present this Citation "

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Vice Admiral Ross F McIntire, (MC), Surgeon General of the U S Navy, commenting on the programs of the War-Time Graduate Medical Meetings in Zone Number Five, recently wrote to the local Chairman, Dr James Alexander Lyon, of Washington "The scope and general interest of the subjects presented, as well as the fact that such outstanding members of the medical profession participated so generously, are noteworthy. This represents a real contribution to the morale and training of the medical officers who have had and are still having the opportunity to profit from these courses

"One hears so often that medical officers on active duty are fearful of getting out of touch with current medical events. These War-Time Graduate Medical Meetings seem to have been designed to anticipate just such a situation, and have succeeded admirably "

## OBITUARIES

## DR MORRIS WEISSBERG

Dr Morris Weissberg, F A C P , died in Brooklyn, New York, on March 17, 1945. Dr Weissberg had been a Fellow of the American College of Physicians since 1926. He was born in Russia in 1887, received his medical degree from the Long Island College Hospital. For many years he was on the Staff of the Bushwick Hospital of Brooklyn, and Attending Physician, Evangelical Deaconess Hospital. He was Consultant to the St. Luke's (Newburgh) Hospital and Evangelical Home for the Aged for a number of years. He served in the first World War as 1st Lieutenant in the A E F , was a member of the Medical Society of the County of Kings, American Heart Association, Brooklyn Society of Internal Medicine, Brooklyn Thoracic Society, American Association for the Advancement of Science, Medical Society of the State of New York, American Legion, Fellow, American Medical Association, New York Academy of Medicine, Diplomate, American Board of Internal Medicine.

Dr Weissberg was a respected member of the profession and his loss will be keenly felt.

ASA L. LINCOLN, M D , F A C P ,  
Governor for Eastern New York

## COLONEL JOHN DIBBLE, (MC), U S A

Colonel John Dibble, (MC), U S Army, was reported "missing in action" during April 1943. It has now been confirmed, through Major General George F. Lull of the Office of the Surgeon General, that Colonel Dibble was definitely lost. He was in a plane which went down in the harbor of a small island in the Pacific, and only two of those aboard the plane survived.

Colonel Dibble was born in Camden, N J , May 24, 1890. He graduated from the University of Pennsylvania School of Medicine in 1915, served an internship at the Episcopal Hospital of Philadelphia, and then entered the Army Medical Corps. He took the regulation course in the Army Medical School and in the Army School for Flight Surgeons. He also took postgraduate work at the Mayo Foundation, and a course in military science and tactics at the Army Command and General Staff School. His tours of duty included assistant, medical service, U S Army General Hospital, Fort Bliss, Texas, post surgeon at various Army Station Hospitals, chief of the tuberculosis section of the Walter Reed General Hospital, executive officer, medical service, Letterman General Hospital, San Francisco, chief of medical service, Station Hospital, Fort McKinley, P I , chief of medical service, Station Hospital Fort Sheridan, Illinois, executive officer, Medical Department, Army Field Service School, medical inspector,



Eighth Corps Area. He was rated as an excellent internist, well qualified in tuberculosis work. He was a Fellow of the American Medical Association and a member of the Association of Military Surgeons of the United States. He had been a Fellow of the American College of Physicians since 1941. He was the first member of the College whose life was lost in the war.

### DR. THOMAS FRANCIS COTTER

Dr. Thomas Francis Cotter, F.A.C.P., Indiana Harbor, Indiana, died March 12, 1945, of pneumonia, aged 67. He was born at Indianapolis in 1877, and graduated from the Medical College of Indiana in 1902. For some years he was a member of the staffs of Mercy and Methodist Hospitals of Gary and at one time was connected with the U. S. Public Health Service. More recently he was a member of St. Catherine's Hospital.

Dr. Cotter was a member of the Lake County Medical Society and the Indiana State Medical Society. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1925. He enjoyed a good reputation in the community where he practiced, both with the public and with the profession.

ROBERT M. MOORL, M.D., F.A.C.P.,  
Governor for Indiana

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